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# HOSPITAL TREATMENT OF PULMONARY TUBERCULOSIS

## A FOLLOW-UP STUDY OF PATIENTS ADMITTED TO EDINBURGH HOSPITALS IN 1953

BY

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This paper reviews the outcome of all cases of adult pulmonary tuberculosis admitted in 1953 to the three tuberculosis hospitals within the City of Edinburgh. The patients have been followed up to the end of 1956, and have therefore been observed for three to four years. Most admissions came via the main chest clinic, which at that time had its own medical staff carrying no responsibility for hospital beds. Waiting-lists were long, and before admission many of the patients had received treatment by regimes of chemotherapy which would now be regarded as undesirable. This accounts for the presence of drug resistance in a significant proportion of the admissions. An element of selection operated because of the size of the waiting-list. Patients responding well to domiciliary and clinic care were not usually admitted to hospital: disappointing clinical response or compelling social factors were often the indication for admission. Some of the patients were admitted virtually moribund.

A reorganization of the tuberculosis service in Edinburgh was being planned in 1953 and came into effect in 1954 (see Discussion). As a step in this reorganization all the patients admitted in 1953 remained after their discharge under the supervision of the clinicians responsible for their hospital care.

The 305 patients studied comprise 156 males and 149 females. The youngest patient was aged 11. Table I shows the age distribution of the patients and the extent of their disease (classification of National Tuberculosis Association of America*). The condition of the patients and their progress since discharge was assessed as at December 31, 1956. If patients had left the area up-to-date information was requested from the clinician to whose care they had passed. There were five patients whose follow-up was incomplete, and these had been observed for periods varying from 11 to 24 months. The remaining patients had been under observation for three to four years.

TABLE I.—*Age Distribution and Extent of Disease of Patients With Pulmonary Tuberculosis Admitted in 1953 to Edinburgh Hospitals*

| Extent of Disease | Age in Years | | | | | | All Ages |
|---|---|---|---|---|---|---|---|
| | 11–19 | 20–29 | 30–39 | 40–49 | 50–59 | 60+ | |
| Far advanced | 14 | 26 | 33 | 24 | 18 | 17 | 132 |
| Moderately advanced | 16 | 57 | 28 | 27 | 11 | 4 | 143 |
| Minimal | 3 | 13 | 9 | 4 | 1 | 0 | 30 |
| All cases | 33 | 96 | 70 | 55 | 30 | 21 | 305 |

### Bacteriology

On admission at least three specimens of sputum were examined by smear and culture. If sputum was unobtainable laryngeal swabs or gastric lavage specimens were cultured. Positive cultures were submitted to tests for sensitivity to streptomycin, P.A.S., and isoniazid.

*Positivity.*—Of the 305 admissions 251 (82%) were bacteriologically positive before treatment. It is probable that this percentage would have been higher had not some patients received drugs before admission to hospital with less adequate preliminary bacteriological search.

*Drug Sensitivity.*—At the time of admission the organisms of the 251 patients with positive bacteriology showed the following sensitivities: sensitive to three standard drugs (streptomycin, P.A.S., and isoniazid), 190; resistant to one of the drugs, 30; resistant to two of the drugs, 19; resistant to three of the drugs, 8; undetermined, 4. Drug resistance could be explained on the basis of unsatisfactory previous chemotherapy in all but eight patients, in whom no history of previous drug treatment could be elicited. It was assumed that they had been infected by a drug-resistant organism. All of these eight patients (3.2% of the cases with positive sputum) had organisms resistant to P.A.S., and the organisms of two were also resistant to streptomycin.

*N.T.A. Classification (1950):

*Minimal.*—"Slight lesions without demonstrable excavation confined to a small part of one or both lungs. The total extent of the lesions, regardless of distribution, shall not exceed the equivalent of volume of lung tissue which lies above the second chondro-sternal junction and the spine of the fourth or body of the fifth thoracic vertebra on one side."

*Moderately Advanced.*—"Slight disseminated lesions which may extend through not more than the volume of one lung or equivalent in both lungs. Dense and confluent lesions which may extend through not more than the equivalent of one-third the volume of one lung. Total diameter of cavities less than 4 cm."

*Far Advanced.*—"Lesions more extensive than moderately advanced."

## Treatment

*Hospital Stay.*—In December, 1956, four of the admissions of 1953 were still in hospital. Among the patients discharged the average stay was ten months.

### Chemotherapy

All patients, with seven exceptions, received chemotherapy. One of the exceptions had been rendered resistant to P.A.S. and isoniazid before admission, and it was thought wise to carry out thoracoplasty without hazarding streptomycin in case resection should subsequently prove necessary. The thoracoplasty controlled the disease. One patient had minimal disease adjudged probably inactive, and drugs were withheld. This patient subsequently relapsed. Five other patients, in a moribund condition when admitted, died without receiving drugs.

Where the patient's organisms were sensitive to the main drugs, regimes of chemotherapy did not differ appreciably from those we use currently. The usual combinations were: (1) Streptomycin 1 g. daily + sodium P.A.S. 5 g. four times daily. (2) Streptomycin 1 g. daily + isoniazid 100 mg. twice daily. (3) Isoniazid 100 mg. twice daily + sodium P.A.S. 10–20 g. daily (two or four doses of 5 g.). (4) A combination of all three drugs, usually as the initial treatment pending the results of sensitivity tests; if these proved satisfactory either streptomycin or P.A.S. was stopped.

In some cases streptomycin was given intermittently (twice or thrice weekly) in combination with daily P.A.S. We have since abandoned this practice, as we believe it carries the danger of the patient's organisms becoming resistant first to P.A.S. and then to streptomycin. There is published evidence of the danger of giving streptomycin intermittently with isoniazid (Medical Research Council, 1953).

In some patients we were faced with the problem of resistance to both streptomycin and P.A.S. In these cases isoniazid was combined with oxytetracycline. The combination of viomycin and oxytetracycline was used for patients resistant to all three of the standard drugs.

Our chemotherapeutic management differed in one important respect from our current practice in that some patients were given drugs for shorter periods than we would now regard as advisable. The importance of this emerges in the study of relapses (see below).

### Minor Collapse Procedures

Five patients (less than 2% of all patients) received treatment with artificial pneumothorax, and 31 (10%) had a pneumoperitoneum induced as a definitive measure and not merely as a preliminary to major surgical measures.

### Major Surgery

During their first period of hospital treatment 122 patients (40% of admissions) underwent major thoracic surgical procedures. They comprised 54 males and 68 females. Thirty-four (28%) were over 40 years of age, and eight (7%) over 50. Of those with far-advanced disease 42% received major surgery, the figures for those with moderately advanced and minimal disease being 44% and 13% respectively. Twenty-two patients had organisms resistant to two drugs or more at the time of surgery. Among the 122 surgically treated cases there were 102 who underwent single procedures; of the 20 patients undergoing multiple procedures nine had surgery directed to both lungs.

The operative procedures, numbering 144, were: 1-stage thoracoplasty, 50; 2-stage thoracoplasty, 4; pneumonectomy, 8; resection of a lobe or more, 37; resection of segments or less, 43; resection of empyema and portion of lung, 2. Six of the thoracoplasty operations were carried out as a preliminary to planned later resection. Thoracoplasty was required in two patients to close a residual space after resection.

Only surgical measures carried out during the first admission as a patient in 1953 are included in the above analysis. Eight patients were submitted to surgery following readmission, and five of these had not had previous surgery.

## Results

The progress of the 305 patients up to December 31, 1956, is summarized in Table II. (The subsequent progress of the patients who relapsed is discussed in a later section.)

TABLE II.—*Pulmonary Tuberculosis Admissions to Edinburgh Hospitals in 1953. Outcome of Treatment, Related to Use of Major Chest Surgery and Sensitivity of Organisms to the Three Standard Drugs While in Hospital*

| State at Discharge | Later Fate | Patients Having: Organisms Sensitive to at Least Two Drugs — Major Surgery | No Surgery | All Cases | Organisms Resistant to at Least Two Drugs — Major Surgery | No Surgery | All Cases | Totals | |
|---|---|---|---|---|---|---|---|---|---|
| Sputum-negative | Remaining well | 95 | 131 | 226 | 13 | 1 | 14 | 240 | 264 |
| | Relapse | 2 | 13 | 15 | 3 | 0 | 3 | 18 | |
| | Death (all causes) | 0 | 5 | 5 | 1 | 0 | 1 | 6 | |
| Sputum-positive | Still positive | 0 | 0 | 0 | 1 | 0 | 1 | 1 | 7 |
| | Lost sight of | 0 | 1 | 1 | 0 | 0 | 0 | 1 | |
| | Now negative and well | 0 | 4 | 4 | 1 | 0 | 1 | 5 | |
| | Death (all causes) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Died in hospital (all causes) | | 3 | 16 | 19 | 3 | 8 | 11 | 30 | |
| Still in hospital | | 0 | 0 | 0 | 0 | 4 | 4 | 4 | |
| Totals | | 100 | 170 | 270 | 22 | 13 | 35 | 305 | |

In this table the expression "sensitive organisms" indicates that the patient's organisms were sensitive in hospital to at least two of the three standard drugs, or that organisms had never been cultured. Resistance to one of the drugs did not exclude a patient from this category, as treatment by a standard and reliable combination of drugs was still possible. A patient's organisms were held to be "resistant" if resistance was shown to be present to at least two of the standard drugs during his period of hospital stay. The same definitions apply to the words "sensitive" and "resistant" when used later. It was, of course, possible for a patient to pass from the "sensitive" to the "resistant" group after discharge from hospital. Similarly, some patients in the "no surgery" category had surgical treatment at a second admission because they had left hospital with their disease uncontrolled or had relapsed after discharge. Table II should be interpreted with these possibilities in mind.

Relapse was defined as evidence of resumed activity of disease after apparent quiescence had been achieved. Such evidence consisted of radiological deterioration, reversion to positive bacteriology, or the development of overt non-pulmonary tuberculosis.

Four of the 305 patients had not been discharged from hospital by the end of December, 1956. All four had been admitted with far-advanced tuberculosis and resistant organisms, and, while the clinical condition of two had not obviously altered, two were undergoing gradual deterioration. All were deemed unfit for surgery, and attempts to treat them by a variety of drugs had so far proved unsuccessful.

*Bacteriological State at Time of Discharge.*—Thirty deaths occurred in hospital and 271 patients were discharged alive, four still being in hospital. Six of the survivors, sputum-negative at the time of discharge, died later from non-tuberculous causes. Among the 271 living discharges there were seven patients whose sputum was still positive (2.6%). One of these patients, who had undergone pneumonectomy but had a persistent broncho-pleuro-cutaneous fistula, was

allowed home with the acquiescence of his physician. Our sputum-positive admissions included 187 patients who (*a*) had drug-sensitive organisms, (*b*) received treatment with a satisfactory combination of standard drugs as described earlier, and (*c*) survived the early post-admission period. With one single exception these patients had been rendered culture-negative within six months of starting drugs; the exceptional case converted to the negative state during the eighth month.

*Irregular Discharge.*—Discharges against medical advice totalled 12 (4% of discharges) and accounted for six of the seven discharges with positive sputum. Reference is made later to the subsequent progress of these patients.

### Deaths

Thirty-six of the 305 patients admitted (12%) had died before the end of December, 1956. The causes of death are shown in Table III:

TABLE III

| | |
|---|---|
| Related to Tuberculosis (26) | |
| Directly attributable | 20 |
| Indirectly | 2 |
| Early post-operative | 4 |
| Due to Non-tuberculous Conditions (10) | |
| Bronchogenic carcinoma | 3 |
| Oesophageal | 1 |
| Leukaemia | 1 |
| Respiratory failure due to ankylosing spondylitis | 1 |
| Cerebral haemorrhage | 2 |
| Chronic nephritis | 1 |
| Cardiovascular degeneration | 1 |

Of the 20 patients whose deaths were directly attributable to tuberculous disease, 15 died from progressive tuberculosis without any obvious associated condtion; one developed congestive failure; one had severe associated emphysema; two had amyloid disease; and one died from haemoptysis. The six deaths indirectly related to tuberculous disease included four post-operative deaths (three from pulmonary insufficiency and one from haemorrhage); one death from torsion of the spleen with retroperitoneal haemorrhage, a complication of pneumoperitoneum treatment; and one death from pneumonia in a patient whose tuberculous disease had been controlled at the cost of extensive fibrosis and grossly impaired lung function.

The time of death after admission is given in Table IV. It will be seen that 9 of the 20 patients whose direct cause of death was tuberculosis died within four weeks of admission.

TABLE IV.—*Time of Death Related to Admission*

| Period After Admission in Months | Deaths Directly Due to Tuberculosis | Deaths from All Causes |
|---|---|---|
| <1 | 9 | 12 |
| 1–5 | 2 | 6 |
| 6–11 | 2 | 3 |
| 12–17 | 2 | 6 |
| Over 18 | 5 | 9 |
| Total | 20 | 36 |

At admission the organisms of the 20 patients whose deaths were directly attributed to tuberculosis showed the following sensitivities: sensitive to streptomycin, P.A.S., and isoniazid, 7; resistant to streptomycin, P.A.S., or isoniazid, 5; resistant to two or more of these drugs, 8.

Of the 12 patients whose organisms were sensitive to at least two of the standard drugs, seven were admitted in a moribund state and died within a month of admission. Another patient, considered to be beyond redemption, was given drugs for only a month. Two further deaths from cardiac failure and amyloid disease occurred in patients whose tuberculous disease was still active at the time of death. Another death from respiratory failure and anoxia was in the main due to associated emphysema, and this patient had been sputum-negative for some months before death. The twelfth patient died from progressive tuberculosis with organisms resistant to all three drugs; the fact that she had been infected with an organism primarily resistant to P.A.S. was not appreciated at the time of admission, and the chemotherapeutic combinations used were inadequate.

### Relapse

Relapse followed in 18 of the 264 patients discharged with negative sputum (7%). In 16 the relapse consisted of a deterioration of the lung condition: 13 had a radiological extension associated with reversion to positive sputum, one had radiological extension only, and two developed a positive sputum culture without apparent radiological change. One patient developed overt spinal tuberculosis and one superficial glandular tuberculosis.

### Factors in Relapse Rate

Some factors were examined which might have an influence on relapse rate.

*Irregular Discharge.*—Six patients taking their discharge against advice had become sputum-negative in hospital, but two of them relapsed.

*Drug Resistance.*—Resistance to two or more of the three standard drugs was present at the time of relapse in four patients (one-fourth of the patients with relapse of pulmonary disease). Three of these were known to have resistant organisms while they were in hospital, but in one resistance became apparent only after discharge. The combination of P.A.S. with intermittent and not daily streptomycin may have been responsible. If it is accepted that this patient had resistant organisms at discharge despite negativity, the relapse rate among sputum-negative discharges with drug resistance was 22% (4 out of 18), as compared with 6% (14 out of 240) among sensitive cases.

*Duration of Chemotherapy.*—Table V is concerned only with surviving patients whose organisms remained sensitive to at least two of the standard drugs, allowing treatment

TABLE V.—*Showing Incidence of Relapse Among Survivors With Organisms Sensitive to Two or More of Standard Drugs, Related to Initial Extent of Disease and Duration of Chemotherapy*

| Duration of Chemotherapy in Months | Extent of Disease | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Far Advanced | | Moderately Advanced | | Minimal | | All Groups | |
| | No. | Relapses | No. | Relapses | No. | Relapses | No. | Relapses |
| <3 | 4 | 2 | 4 | 1 | 6 | 2 | 14 | 5 (35·7%) |
| 3–5 | 3 | 2 | 4 | 0 | 5 | 0 | 12 | 2 (16·7%) |
| 6–8 | 4 | 0 | 23 | 2 | 4 | 0 | 31 | 2 (6·5%) |
| 9–11 | 11 | 1 | 31 | 3 | 6 | 0 | 48 | 4 (8·3%) |
| 12–17 | 26 | 1 | 43 | 0 | 4 | 0 | 73 | 1 (1·4%) |
| 18–23 | 14 | 0 | 12 | 0 | 0 | 0 | 26 | 0 |
| 24+ | 21 | 0 | 14 | 0 | 2 | 0 | 37 | 0 |
| Total | 83 | 6 (7·2%) | 131 | 6 (4·6%) | 27 | 2 (7·4%) | 241* | 14 (5·8%) |

* The number of patients discharged sputum-negative with known or presumed sensitive organisms was 240. Two patients discharged sputum-positive had sensitive organisms and achieved negativity with continued chemotherapy as out-patients, and are included in the Table. One patient is omitted from the Table because he took drugs very irregularly after discharge and no reasonably accurate assessment of the duration of chemotherapy was possible. No relapse cases have been omitted.

with reliable combinations of streptomycin, P.A.S., and/or isoniazid. The relapse experience is shown for groups receiving chemotherapy for different periods. Although the figures are small there is a definite trend, with an inverse relationship between relapse experience and duration of chemotherapy. Five out of 14 patients receiving drugs for less than three months relapsed. Among the 63 patients treated for more than 18 months no relapses occurred, and there was only one relapse among the 136 patients given drugs for more than a year. The actual duration of chemotherapy in this case was 15 months. While the patients receiving the longer periods of drug treatment have had a shorter average period of observation since drugs were stopped, this would not by itself explain the different relapse experience.

The duration of drug treatment appears even more important when considered in relation to the extent of disease.

#### Extent of Disease

In the pre-chemotherapy era the relationship between the original extent of lung disease and the likelihood of later relapse was well recognized. Such a relationship was not immediately apparent in a study of our drug-sensitive cases. Table V shows that relapse was observed in 7.2% of patients with far advanced disease, 4.6% of moderately advanced cases, and 7.4% of minimal cases. Also apparent from the table, however, is the trend towards longer periods of drug treatment with more extensive disease.

The percentage relapse rates in the final column of Table V were used to calculate the number of relapses which would be expected in the far-advanced, moderately advanced, and minimal groups if extent of disease had no relation to later relapse experience. The "expected" relapses among far-advanced cases were 3.5 (actually observed 6), among moderately advanced 6.8 (observed 6), and among minimal cases 3.8 (observed 2). The calculations are consistent with the hypothesis that the worse prognosis associated with more extensive disease was masked by the use of relatively longer periods of chemotherapy.

### Major Surgery

The part played by thoracic surgery can perhaps be best assessed by considering patients with sensitive and resistant organisms separately (see Table II).

#### Patients with Resistant Organisms

Among 22 resistant cases undergoing surgery there were four deaths (two post-operative, one from progressive tuberculosis, and one from pneumonia). Among the 18 survivors 16 were discharged sputum-negative, but three relapses occurred. The 13 resistant cases not submitted to surgery had a much less favourable experience. Only one was discharged sputum-negative, and eight have died as a result of their tuberculosis.

#### Patients with Sensitive Organisms

Of 100 patients with sensitive organisms receiving surgery, 97 were discharged sputum-negative and only two of these relapsed. Out of the 144 patients not treated surgically and discharged sputum-negative, 13 relapsed.

The more favourable experience of the surgically treated patients with sensitive organisms cannot be wholly attributed to surgery. In 1953 there was a waiting period for surgery, and in consequence surgically treated patients received on average longer periods of chemotherapy. To adjust for duration of chemotherapy and extent of original disease, separate tables in the same form as Table V were constructed for surgical and non-surgical patients and were used to calculate "expected" relapses in the corresponding groups of surgically treated patients. By summation it was found that the "expected" number of relapses among the surgical patients, assuming no effect from surgery, was 4.5. This compares with the observed number of two relapses. The difference is slight and the value of surgery *per se* in patients with drug-sensitive organisms cannot be considered to have been proved. But these calculations do not take into account the factor of clinical selection for surgery. Presumably many of the patients with sensitive organisms were submitted to surgery because there were features which suggested a greater likelihood of relapse, though, on the other hand, some might have been denied surgery because of poor respiratory function.

### Later Fate of Patients Who Relapsed

Seventeen of the 18 patients who relapsed were readmitted and one was treated at home. All received further chemotherapy, and five had surgical procedures. By December, 1956, all but one had been rendered sputum-negative. Thirteen were at work and two were fit for work but in normal retirement. (Two patients, in hospital in December, 1956, have since been discharged and are also at work at the time of writing.)

### Later Fate of Patients Sputum-Positive on Discharge

The seven patients who were discharged with positive sputum (six of them against advice) were all given further treatment. The six irregularly discharged patients had sensitive organisms while in hospital, and two achieved bacterial negativity and quiescence of disease without further treatment than chemotherapy, for which one was readmitted. Three patients, two of whom had developed resistant organisms while out of hospital (almost certainly from failure to take drugs as prescribed), were rendered sputum-negative with the aid of surgery. One patient left the district on discharge and was still sputum-positive eight months later, since when no knowledge concerning him has been available.

The condition of the single sputum-positive patient given a regular discharge has not altered.

### General Assessment of Patients at December 31, 1596

#### Bacteriological

Six of the 269 survivors (2.2%) were known to be sputum-positive in December, 1956. Five of these patients were in hospital, four having been under continuous hospital treatment and one having been readmitted following relapse. Only one patient was at home with a known positive sputum.

#### Work Status

A survey of 269 patients in December, 1956, gave the findings shown in Table VI:

TABLE VI

| | | |
|---|---|---|
| *Fit for work:* | | |
| Working or normal retirement | 243 | 250 (93%) |
| Unemployed | 7 | |
| *Unfit for work because of tuberculosis:* | | |
| At home | 5 | 11 (4%) |
| In hospital | 6 | |
| *Unfit owing to non-tuberculous disease* | | 8 (3%) |

By the time of writing two of the patients in hospital in December, 1956, had been discharged and were at work, so that only 3.4% of the surviving patients were unfit for work as a direct consequence of tuberculosis.

### Discussion

In the past 10 years any attempt to assess results in the treatment of pulmonary tuberculosis has suffered from an important difficulty. A major criterion of success is the absence of relapse, so that a reasonable period of follow-up is essential; but at the end of such a period the original methods of treatment are apt to be out of date. Our assessment of the results of hospital treatment of patients admitted in 1953 has the advantage that, though we have been able to follow up our patients for a minimum of three years, our general methods of chemotherapy have not radically changed during that period. By 1953 Medical Research Council trials, and studies in our own hospitals, had established combinations of drugs which prevented the emergence of drug-resistant tubercle bacilli in almost all patients, provided they had not previously received unsatisfactory chemotherapy or been infected with resistant organisms. We were also beginning to appreciate the advantages of chemotherapy on a prolonged basis, even though the duration of treatment given to our 1953 patients was not always as long as would be our current practice.

The proportion of patients treated surgically in 1953 was much higher than would now be the case in our hospitals. This can be attributed in part to the higher prevalence of drug-resistant organisms among admissions in 1953, and we had not yet acquired as much confidence as we now possess in the ultimate results of chemotherapy unsupplemented by other measures.

#### Deaths

Although the overall mortality among our patients was 12%, some was attributable to non-tuberculous disease, and

the true death rate from tuberculosis was 8.6%. When post-operative deaths and deaths related to tuberculosis but not directly attributable are excluded, it is noteworthy that nearly half of the tuberculous deaths occurred within a month of admission—that is to say, in patients admitted moribund. Eight of the 20 patients dying directly from tuberculous disease had organisms which were resistant to two or more of the standard three drugs on admission.

The main factors contributing to our tuberculous deaths were therefore delayed admission and drug resistance. Both these factors should be preventable or almost so, and we believe that under present conditions deaths due to progressive tuberculous disease should be few indeed. No doubt the pulmonary fibrosis associated with the healing of the tuberculous process will claim its ultimate toll of death from cor pulmonale, and we may also expect an occasional death from the acute, almost accidental, complications of lung tuberculosis—haemoptysis and spontaneous pneumothorax.

Post-operative death rates have little meaning except in reference to the type of the patient submitted to surgery. Our surgical patients included a relatively large proportion of seriously ill cases whose outlook without surgery was regarded as hopeless. A sixth of them had organisms resistant to two or more of the standard drugs. Our surgical colleagues deserve great credit for their willingness to come to our aid in the treatment of some desperately ill patients. In the circumstances the early post-operative mortality of 3% (patients and not procedures) was remarkably low.

### Relapses

In most reports relating to the prognosis of tuberculosis the majority of relapses have been observed within two years of leaving hospital. Our relapse rate among survivors was 7%, which compares favourably with other published reports but is still, we believe, unsatisfactorily high.

Our analysis of relapses indicates the importance of drug resistance as a factor. When resistance to two or more of the standard drugs was present before apparent quiescence with negative sputum was obtained, relapse followed in 22% of patients, while among sensitive cases the proportion relapsing was 6%.

In our patients with drug-sensitive organisms the most important single factor in reducing the risks of relapse appeared to be the duration of chemotherapy. The recognized relationship between relapse and extent of original disease was concealed by the tendency to give longer drug treatment to patients with more extensive disease. No patient receiving more than 15 months of chemotherapy relapsed. The shorter the period of drug treatment the greater was the likelihood of relapse. This inverse relationship between relapse and duration of chemotherapy is entirely consistent with other investigations carried out in Edinburgh. Ross and Kay (1956), studying patients whose cavities had closed under chemotherapy, did not observe any relapses among patients whose drugs had been continued for more than six months after cavity closure. Stewart and her colleagues (1956), in their studies of resected lung specimens, found an inverse relationship between the duration of effective chemotherapy and the recovery of viable tubercle bacilli from the lung.

### The Role of Surgery

Our drug-resistant cases submitted to surgery fared vastly better than did our other drug-resistant patients. Patients who were denied surgery were, of course, more gravely ill. Even so, the results of surgical treatment in drug-resistant cases leave us in no doubt that drug resistance, far from being a contraindication to surgery as so commonly suggested, constitutes in fact a compelling argument for its use, if the patient is reasonably fit. While some of the recently introduced drugs are less efficient than streptomycin, P.A.S., and isoniazid, operative procedures can be carried out successfully under their cover.

The place of surgery in the treatment of patients with sensitive organisms is less certain. Our surgical patients did well and only 2% relapsed. In addition to surgery, however, they received longer periods of chemotherapy than did the non-surgical patients, and we were unable to exclude the possibility that prolonged chemotherapy and not surgery *per se* was responsible for their favourable experience. It can be argued that the group of patients with sensitive organisms submitted to surgery were chosen because the clinicians regarded relapse as a probable event without its use, and that in consequence the low relapse rate observed among the surgical patients is sufficient evidence of the value of surgery. But we cannot be certain that the clinicians were correct in their judgment. Experience in the pre-chemotherapy era has led us to view features such as unclosed and blocked cavities with the utmost suspicion and as indications for surgical treatment, but the possibility exists that the use of modern drugs for prolonged periods may have robbed even these of their menace. The place of surgery needs reappraisal in the light of new developments. Retrospective studies suffer from the inescapable element of selection, and the value of surgery could best be defined by controlled trial, with random allocation of patients to surgical and non-surgical groups when the clinicians thought such a course justifiable, and with both groups receiving similar chemotherapy on a prolonged basis.

### Resettlement of Patients

Our patients may be considered to have done well in re-establishing themselves in society after discharge. In December, 1956, only 4% of the survivors were unfit for work by virtue of tuberculosis, and among those capable of work less than 3% had failed to find employment.

The tuberculosis hospital has an important part to play in reducing the pool of known infectors at large in the community. As few patients as possible should be discharged in an infectious state. Seven of our patients (2.6% of survivors) were discharged with a positive sputum, but six of them had taken their own discharge. Irregular discharge is obviously an important problem but should be less frequent under present conditions than it was in the past. Improved prognosis, shorter hospital stays, and financial aid must all help to reduce the incidence of irregular discharge. We are unaware of any earlier reported hospital series with as low an irregular discharge rate as the 4% observed.

Patients discharged irregularly or with positive sputum remained under our clinical supervision and some were re-admitted. The response to further treatment measures was satisfactory and at the time of follow-up only one of our series of patients was known to be outside hospital with a positive sputum, though we lacked information about another one who was positive but had left the district and was untraced.

In the patient with drug-sensitive organisms the attainment of sputum negativity poses little problem. Even in far-advanced cases sputum conversion can confidently be expected if a reliable and appropriate combination[2] of drugs is administered (Horne and Grant, 1956). All patients meeting these conditions among our admissions of 1953 achieved the culture-negative state, and, with the exception of the patient who converted in the eighth month, all became negative within six months of starting drugs.

### Current Tuberculosis Practice in Edinburgh

Reorganization of the Edinburgh tuberculosis services in January, 1954, resulted in the allocation of both clinic and hospital duties to all consultants. The arrangements allowed each patient to remain under the care of the same consultant from entry to the register until his removal. We believe that the continuity of supervision thus achieved has been to the benefit of the patients, and there has been a more rapid turnover of hospital beds. A hospital waiting-list of 375 patients in March, 1954, had been all but eliminated a year later.

Any patient with a positive sputum is normally admitted to hospital and retained at least until the sputum becomes negative on culture. Patients with negative bacteriology, mild disease, and insignificant symptoms are often treated on an out-patient basis and are usually allowed to continue at work. Very few patients are treated at home on bed rest.

In the case of previously untreated patients admitted to hospital it has been our practice for some time to initiate treatment with all three standard drugs. It is known that a small but important proportion of new tuberculous cases have been infected with tubercle bacilli resistant to one of the main drugs (Thomas *et al.*, 1954; Fox *et al.*, 1957). The number with organisms resistant to two drugs is much smaller. A two-drug regime involves the risk of losing the benefit of a second drug should it be combined with a drug to which the patient's organisms are already resistant. The danger of reducing resistance is not completely circumvented by the use of a triple-drug regime, but on balance there are advantages in its use.

Patients under 40 years of age receive streptomycin 1 g. in a single injection daily, together with sodium P.A.S. 5 g., and isoniazid 100 mg., both given twice daily by mouth. If sensitivity tests on pre-treatment cultures are satisfactory in respect of all three drugs, either P.A.S. or streptomycin is withdrawn. Our standards of drug sensitivity are high, and any degree of resistance above the threshold of experimental error is considered of potential clinical significance. Solid media are used for sensitivity tests (Stewart, 1955).

Because of the increased risk of vestibular disturbance patients over 40 years of age are not given streptomycin daily, but as 1 g. three times weekly in combination with P.A.S. and isoniazid. When the patient is discharged from hospital, treatment is usually continued with P.A.S. and isoniazid because of the inconvenience of giving streptomycin injections on a domiciliary basis. The P.A.S. and isoniazid are given in the same doses as before in the form of cachets containing both drugs, so that the patient cannot take one drug without the other.

We are wary about resorting to drugs claimed by the manufacturers to be effective substitutes for the standard drugs and advocated because of lower toxicity. We believe that such drugs should not be used routinely until they have been shown to produce adequate blood or urine levels of their active components. The drug claimed to possess a new action should be submitted to a carefully conducted trial before it is accepted for routine use.

Even the minimal case receives uninterrupted chemotherapy for at least a year. In general our practice is to give drugs for at least a year after sputum conversion, cavity closure, or operation, whichever is the latest. Severe cases, or patients with residual open cavities, are treated for at least two years.

Patients admitted desperately ill in grave danger of early death are treated with corticosteroids in addition to chemotherapy. Subjective improvement is more rapid and survival of the patient may be obtained until the effect of the chemotherapeutic drugs is apparent. The place of corticosteroids in routine treatment has been recently assessed (Research Committee of Tuberculosis Society of Scotland, 1957). Corticosteroid drugs must, of course, always be covered by chemotherapy to which the patient's bacilli are sensitive.

Mild cases with negative sputum treated at work without hospital admission usually receive P.A.S. and isoniazid in combined cachet form. The vital importance of taking drugs regularly and in the prescribed dosage is explained carefully to patients receiving treatment out of hospital. Even so, an occasional bitter experience has taught us not always to rely on a patient's veracity, and it is wise to check the urine for P.A.S. from time to time (Simpson, 1956).

Artificial pneumothorax has been abandoned, and the place of pneumoperitoneum in routine treatment is under assessment. Cavities which fail to close on chemotherapy are usually dealt with by resection, but if this entails a significant operative risk we are prepared to treat the patient with chemotherapy alone. Some of the excellent results in such patients have already been reported (Douglas and Horne, 1956). We seldom recommend resection of lesions without overt cavitation unless we suspect that the patient will fail to co-operate adequately in a prolonged chemotherapy programme after discharge. Totally destroyed lungs, extensive basal tuberculous bronchiectasis, and narrow stricture of a lower-lobe bronchus we regard as definite indications for resection. It is our opinion that surgery has its largest part to play in the treatment of patients who are producing organisms rendered resistant by previous unsatisfactory chemotherapy. In these patients various forms of "salvage" chemotherapy have to be employed, mainly with the object of making the patient fit for operation and preventing post-operative complications (Crofton, 1955; Stewart *et al.*, 1954; Murdoch and Stewart, 1956; Stewart *et al.*, 1957).

We consider that the weapons now available are sufficient to command recovery in nearly all newly diagnosed cases of pulmonary tuberculosis. One hundred per cent. success is not an unreasonable target. Failure can almost always be traced to errors committed by the doctor or by the patient, the doctor failing to prescribe reliable combinations of drugs or the patient failing to take his drugs as prescribed. It should not be accepted with complacency, and its explanation should be assiduously sought.

## Summary

The types of treatment given to 305 patients with pulmonary tuberculosis admitted in 1953 to the Edinburgh tuberculosis hospitals are described and the results achieved are assessed up to December, 1956.

The death rate from tuberculosis was 8.6%. Drug resistance and admission in a moribund state accounted for most of the tuberculosis deaths in this series. As these are largely preventable, deaths from progressive tuberculosis should be rare.

Of the survivors 7% relapsed during the period under review. Important factors in determining relapse were drug resistance and the duration of chemotherapy. There have been no relapses among 63 patients with sensitive organisms receiving more than eighteen months' chemotherapy.

The condition of the patients in December, 1956, is described with particular reference to their employment status and infectiousness. Only 4% of survivors were unfit for work by virtue of tuberculosis.

Our current practice in the treatment of pulmonary tuberculosis is summarized.

The work here reported would have been impossible without the skilled help of numerous colleagues. In particular we should like to thank our surgical colleagues, Messrs. A. Logan, J. D. Wade, R. J. M. McCormack, and P. Walbaum; our bacteriologists, Dr. A. T. Wallace, Miss Sheila Stewart, and their technical assistants; our registrars and other medical assistants; and finally the nursing staff, on whom so much depended. Most of the research on which our chemotherapy was founded was financed by a generous grant from the Royal Victoria Hospital Tuberculosis Trust.

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# PREDNISOLONE COMPARED WITH CORTISONE IN TREATMENT OF CHILDREN WITH CHRONIC ASTHMA

BY

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In a previous investigation (Kennedy and Thursby-Pelham, 1956) we reported the effect of oral cortisone on the ventilatory function of children with chronic asthma. We have now completed a similar investigation using prednisolone, and the relative efficacy of the two drugs can be compared.

In the previous investigation 12 children who had asthma associated with poor ventilatory function were given a trial course of cortisone by mouth. The effects on the ventilatory function of each child were compared with those obtained with a similar course of placebo tablets. In the present investigation 12 children who had a trial course of cortisone six to nine months previously were given a similar course of prednisolone, using one-fifth of the dose of cortisone, and the results of the two treatment regimes are presented.

## Present Investigation

*Children Studied.*—The 12 children selected from the asthma clinic for treatment with prednisolone had all had a controlled trial on cortisone. Six of these (Cases 37, 11, 26, 23, 44, and 62) were reported in our previous communication, and a further six had a similar trial at a later date. Only those children who could attend the clinic twice weekly and who would co-operate in the breathing tests were selected. There were 10 boys and 2 girls, whose ages ranged from 9 to 15 years. All had been under observation for not less than six months and had been found to have impaired ventilatory function between their acute attacks and when free from symptoms. Table I briefly summarizes the cases.

*Method of Assessment.*—As in the previous investigation, we have measured the expiratory flow rate over the first 0.75 second of expiration (E.F.R.[40]) as described by Kennedy (1953). This measure is an index of the maximum ventilatory capacity at the theoretical breathing rate of 40 breaths a minute. All the children attended the clinic twice weekly, and at each attendance the E.F.R.[40] was measured with a spirometer before and after a five-minute inhalation of adrenaline (1 in 1,000).

TABLE I.—*Summary of Children Studied (At the Beginning of the Investigation)*

| Case No. | Sex and Age | Duration of Asthma (Years) | Approx. Frequency of Acute Attacks | History of Other Allergy | Predominant Type of Asthma | * |
|---|---|---|---|---|---|---|
| 80 | M 10 | 2 | Weekly | None | Allergic + psychological | 74% |
| 5 | M 14 | 13 | 3 a year | Infantile eczema | ,, ,, | 65% |
| 78 | M 13 | 13 | 4 ,, ,, | None | Allergic | 44% |
| 20 | M 9 | 7 | 2–3 a year | Infantile eczema | Allergic + infective | 51% |
| 43 | M 13 | 10 | Monthly | Eczema, hay-fever | Allergic | 49% |
| 25 | M 9 | 5 | 2–3 a month | Eczema | ,, | 72% |
| 37 | M 10 | 6 | 6 a year | None | ,, | 65% |
| 23 | M 12 | 11 | 6–9 a year | Eczema, hay-fever | Allergic + infective | 59% |
| 62 | M 13 | 12 | Monthly | None | ,, ,, | 42% |
| 44 | F 15 | 8 | 2–3 a month | Eczema | Allergic + psychological | 27% |
| 26 | F 10 | 3 | 2–3 ,, ,, | Hay-fever | ,, ,, | 88% |
| 31 | M 13 | 3 | Monthly | None | Allergic + infective | 50% |

*$\frac{\text{Mean E.F.R.}^{40}}{\text{Predicted normal E.F.R.}^{40}} \times 100$

## Treatment Regime

*Cortisone Trial.*—Each course consisted of 100 tablets. The cortisone tablets were 25 mg. each, and the placebo tablets, which were indistinguishable from the cortisone, consisted of lactose with a trace of quinine. Dosage: five cases (Nos. 5, 78, 20, 43, and 25) received 75 mg. of cortisone daily for two weeks, followed by 62.5 mg. daily in divided doses for the rest of the course. Seven cases (Nos. 80, 31, 26, 23, 44, 62, and 37) received 75 mg. daily for two or three weeks and then 50 mg. daily in divided doses for the rest of the course.

*Prednisolone Trial.*—Prednisolone was prescribed as 5-mg. tablets. All the above cases had a course lasting six weeks. For the first three weeks the dose was 15 mg. of prednisolone daily (5 mg. t.d.s.), and for the remaining three weeks the dose was reduced to 10 mg. daily (5 mg. b.d.). 75 mg. of cortisone daily or 15 mg. of prednisolone daily are hereafter referred to as *full dosage*, as no higher doses were used in these trials. 62.5 mg. and 50 mg. of cortisone and 10 mg. of prednisolone are referred to as *reduced dosage*.

The courses of cortisone were preceded or followed by a course of placebo in a blind trial. The results showed variable amounts of improvement on cortisone, and it was noteworthy that none showed a better response to placebo. As the effects of suggestion were ruled out by this means, the course of placebo was not repeated in the prednisolone trial, which was compared with the readings obtained during the preceding two months, when the patients received no treatment except the adrenaline inhalations associated with the routine tests.

## Symptomatic Results

The general effects produced by prednisolone therapy were similar to those produced by cortisone. During both trials all the children except two had a marked increase in appetite and weight. These two cases failed to gain weight while taking either prednisolone or cortisone. The rest showed weight increases of 2 to 10 lb. (0.9 to 4.5 kg.) on cortisone and 2 to 12 lb. (0.9 to 5.4 kg.) on prednisolone. The mean weight gain in both trials was 4 lb. (1.8 kg.). Both steroids produced a general increase in well-being and energy in all the cases.

Salt was not restricted during the prednisolone trial. The knowledge that sodium retention was unlikely to be produced by prednisolone encouraged us to continue the higher dose level for a longer period than with cortisone, though in fact neither oedema nor hypertension was observed during either treatment regime. Most of the 12 children studied were free from asthmatic symptoms, such as wheezing and coughing, while on full doses, though about half had symptoms while on reduced doses. On prednisolone, 15 mg. daily, only one child had asthmatic symptoms, whereas three had some symptoms recorded while on the equivalent dose of cortisone, 75 mg. daily. The number of children who were free of asthmatic symptoms during treatment with cortisone and with prednisolone are shown in Table II.

TABLE II

| | No. in Trial | No. of Children Free of Asthmatic Symptoms | |
|---|---|---|---|
| | | On Full Dosage | On Reduced Dosage |
| Cortisone trial .. .. | 12 | 9 | 7 |
| Prednisolone trial .. | 12 | 11 | 6 |

N.B. Same 12 children in both cortisone and prednisolone trials.

## Ventilatory Function Before and After Treatment

### Overall Response of Individuals

The mean E.F.R.[40] values of the individual children recorded during the administration of placebo tablets and the mean values recorded during treatment with cortisone are compared in Table III. Similarly, in Table IV, the mean values obtained during treatment with prednisolone are compared with those obtained during a control period. The difference between the control or placebo E.F.R.[40] value and the mean E.F.R.[40] during treatment has been expressed as a percentage of the control value to provide a measure of the response to the drug under trial. Tables III and IV show the response of individual children to adrenaline and cortisone or prednisolone, and also the combined effect of adrenaline and the steroid under trial. On comparing the results of cortisone and prednisolone, we found that two of the 12 children (Cases 5 and 25) responded better (by 10% or more) to cortisone, whereas 7 (Cases 80, 20, 43, 37, 62, 44, and 46) responded better to prednisolone. The adrenaline response is much the same in the two trials, whether given alone or in addition to either cortisone or prednisolone.

### Overall Response of Group

The mean overall response of the 12 children to cortisone and prednisolone, as judged by the E.F.R.[40] results, has been extracted from Tables III and IV and is given in Table V.

The duration of the equivalent dose levels of cortisone and prednisolone varied slightly—namely, the cortisone dose was usually reduced after two weeks, whereas prednisolone was reduced after three weeks. This might account for the greater overall response to prednisolone. A more valid comparison was made when their effects were compared at definite time intervals.

TABLE V.—*Percentage Change in the Mean E.F.R.[40] Values of 12 Children*

| Cortisone Trial | | | Prednisolone Trial | | |
|---|---|---|---|---|---|
| Adrenaline | Cortisone | Cortisone and Adrenaline | Adrenaline | Prednisolone | Prednisolone and Adrenaline |
| +14% (Nil–29%) | +21% (Nil–67%) | +38% (13–75%) | +16% (4–29%) | +31% (11–64%) | +52% (33–82%) |

### Group Response Related to Time and Dose

Fig. 1 shows the mean E.F.R.[40] values of nine children who had comparative data at weekly intervals, first during treatment with cortisone and later with prednisolone. The baseline values for the two trials have been taken from the average reading during the respective control periods. They are not the same in the two trials because the prednisolone trial was carried out six to nine months after the cortisone trial, when the children were older and larger. For the same reason the predicted normal E.F.R.[40] value differs in the two trials. The predicted normal E.F.R.[40] values are calculated from the height and age, using the following formula (Kennedy, Thursby-Pelham, and Oldham, 1957):

$$\text{The predicted E.F.R.}^{40}\ (\text{l./min.}) = 3.23 \times X_1 + 2.41 \times X_2 - 135$$

where $X_1$ = height in inches

$X_2$ = age in years.

The absolute values of the E.F.R.[40] given in Fig. 1 shows that the group achieves its highest response to full doses of cortisone and prednisolone during the second and third weeks of treatment (cortisone was not administered to the whole group during the third week). When the dose is reduced the response wanes, and two weeks after the cessation of cortisone and prednisolone treatment the absolute

TABLE III.—*Twelve Children with Ventilatory Insufficiency. E.F.R.[40] Values, Before and After Adrenaline Inhalations and During Treatment with Placebo and with Cortisone*

| Case No. | Oral Placebo | | | Oral Cortisone | | | Response to Adrenaline $\frac{b-a}{a}\times 100$ | Response to Cortisone $\frac{c-a}{a}\times 100$ | Response to Cortisone + Adrenaline $\frac{d-a}{a}\times 100$ |
|---|---|---|---|---|---|---|---|---|---|
| | No. of Readings | E.F.R.[40] l. min. | | No. of Readings | E.F.R.[40] l. min. | | | | |
| | | Before Adrenaline a | After Adrenaline b | | Before Adrenaline c | After Adrenaline d | | | |
| 80* | 10 | 42 (33–48) | 44 (34–53) | 10 | 54 (51–58) | 54 (44–59) | +7% | +26% | +26% |
| 5* | 11 | 51 (32–68) | 62 (33–72) | 11 | 64 (56–76) | 76 (67–80) | +22% | +25% | +49% |
| 78* | 13 | 36 (28–48) | 41 (33–48) | 11 | 60 (44–79) | 63 (46–77) | +14% | +67% | +75% |
| 20 | 7 | 29 (20–33) | 31 (23–37) | 15 | 29 (20–40) | 36 (23–44) | +7% | Nil | +24% |
| 43* | 14 | 35 (23–60) | 40 (27–55) | 11 | 35 (24–50) | 42 (30–60) | +14% | .. | +20% |
| 25* | 11 | 44 (22–62) | 56 (30–64) | 10 | 55 (40–66) | 69 (53–77) | +14% | +25% | +57% |
| 37* | 10 | 45 (34–50) | 46 (37–57) | 14 | 47 (34–68) | 51 (44–66) | +2% | +4% | +13% |
| 23* | 16 | 64 (53–80) | 77 (61–103) | 12 | 79 (66–96) | 89 (81–96) | +20% | +23% | +39% |
| 62 | 10 | 44 (32–59) | 44 (29–57) | 12 | 57 (37–79) | 67 (39–79) | Nil | +30% | +52% |
| 44 | 10 | 26 (18–37) | 31 (22–44) | 6 | 28 (19–35) | 35 (30–46) | +19% | +8% | +35% |
| 26* | 5 | 46 (40–52) | 55 (50–62) | 9 | 53 (50–57) | 59 (52–66) | +20% | +15% | +28% |
| 31 | 8 | 42 (30–59) | 53 (33–68) | 14 | 61 (27–82) | 68 (48–92) | +29% | +30% | +45% |
| | | | | | | Mean | +14% | +21% | +38% |

* Patients in whom placebo followed cortisone.

TABLE IV.—*Twelve Children with Ventilatory Insufficiency. E.F.R.[40] Values, Before and After Adrenaline Inhalations, During Treatment with Prednisolone, and During a Comparable Control Period*

| Case No. | Control Period | | | Oral Prednisolone | | | Response to Adrenaline $\frac{x-w}{w}\times 100$ | Response to Prednisolone $\frac{y-w}{w}\times 100$ | Response to Prednisolone + Adrenaline $\frac{z-w}{w}\times 100$ |
|---|---|---|---|---|---|---|---|---|---|
| | No. of Readings | E.F.R.[40] l. min. | | No. of Readings | E.F.R.[40] l. min. | | | | |
| | | Before Adrenaline w | After Adrenaline x | | Before Adrenaline y | After Adrenaline z | | | |
| 80 | 7 | 43 (41–48) | 49 (46–57) | 12 | 63 (46–70) | 69 (48–75) | +14% | +46% | +60% |
| 5 | 10 | 61 (50–70) | 70 (56–77) | 11 | 68 (56–81) | 81 (70–86) | +15% | +11% | +33% |
| 78 | 10 | 50 (40–68) | 56 (44–78) | 11 | 82 (58–101) | 85 (57–106) | +12% | +64% | +70% |
| 20 | 12 | 35 (18–45) | 39 (23–55) | 11 | 47 (32–35) | 54 (40–60) | +11% | +34% | +54% |
| 43 | 10 | 45 (35–55) | 47 (36–55) | 8 | 55 (50–61) | 63 (53–74) | +4% | +22% | +40% |
| 25 | 10 | 47 (37–58) | 54 (44–62) | 11 | 54 (28–68) | 69 (36–79) | +15% | +15% | +41% |
| 37 | 10 | 44 (40–51) | 52 (46–57) | 10 | 51 (44–62) | 61 (55–72) | +18% | +16% | +39% |
| 23 | 11 | 71 (55–86) | 82 (68–92) | 11 | 83 (55–110) | 96 (77–105) | +15% | +17% | +35% |
| 62 | 7 | 45 (31–46) | 55 (42–73) | 7 | 64 (52–84) | 76 (57–92) | +22% | +42% | +69% |
| 44 | 10 | 28 (22–37) | 36 (31–43) | 10 | 39 (24–51) | 51 (26–64) | +29% | +39% | +82% |
| 26 | 11 | 65 (42–70) | 69 (58–77) | 11 | 68 (61–72) | 81 (77–88) | +23% | +21% | +45% |
| 31 | 10 | 52 (39–70) | 58 (40–79) | 9 | 76 (50–88) | 82 (56–92) | +12% | +46% | +58% |
| | | | | | | Mean | +16% | +31% | +52% |

E.F.R.[40] values for the group were almost back to their pretreatment or baseline level. Although the group as a whole does not reach the predicted normal value during treatment, it is shown below that a number of individuals achieved their predicted normal values at the height of their response.

The group response to aerosol adrenaline was interesting—the highest response in *both* trials occurred during the one to two weeks post-treatment period, whereas the adrenaline response was reduced to less than the pretreatment level during the first week on prednisolone and the first two weeks on cortisone. During the remaining weekly periods on treatment the adrenaline response was enhanced.

In Fig. 2 the response of the same nine children to the two drugs is compared by expressing the results as a percentage increase in the E.F.R.[40] over a baseline value. On the whole, the results are remarkably similar. It appears that prednisolone is more effective during the first week, whereas cortisone is more effective during the second week. Prednisolone showed a further response in the third week on full dosage, but there were no comparable data for cortisone.

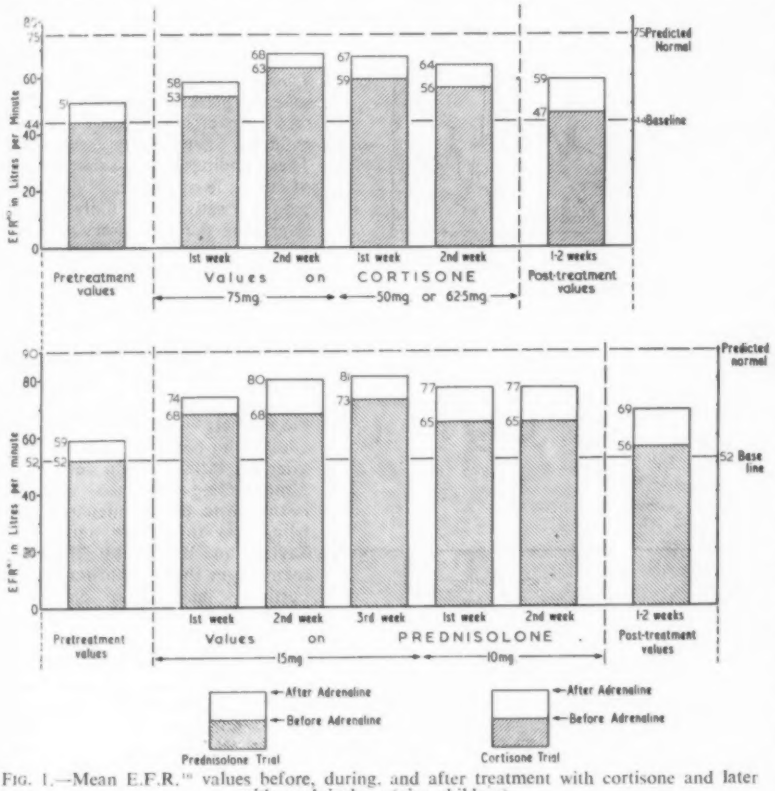


FIG. 1.—Mean E.F.R.[40] values before, during, and after treatment with cortisone and later with prednisolone (nine children).

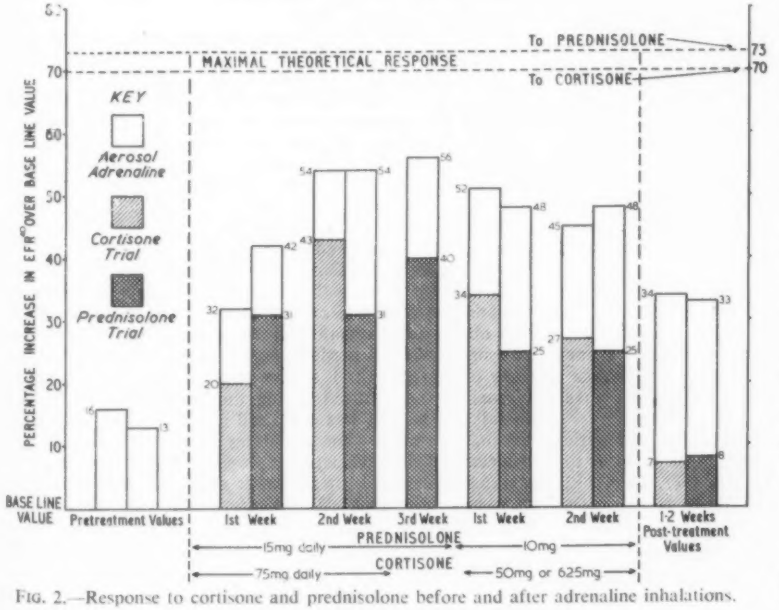


FIG. 2.—Response to cortisone and prednisolone before and after adrenaline inhalations.

### Individual Response Related to Time and Dose

Fig. 3 shows the E.F.R.[40] values recorded over the period of two years in Case 78. The vertical line above each reading plotted on the graph represents the increase in E.F.R.[40] after adrenaline inhalations. The response of oral cortisone and oral prednisolone is demonstrated. A course of long-acting corticotrophin Z, 40 units intramuscularly three times weekly, is shown for comparison.

It will be seen that the E.F.R.[40] in Fig. 3 approaches the predicted normal for a boy of the same height and age only when he is on cortisone, prednisolone, or corticotrophin. The first course of cortisone (October, 1955) produced a good response, and his E.F.R.[40] rose almost to his predicted normal value. The second course of cortisone (January and February, 1956), which was started as a lower dose, was not so effective. It is interesting to see that the response to long-acting corticotrophin is very similar in time and magnitude to prednisolone.

From a study of the individual graphs of the 12 children it was seen that with the doses used the E.F.R.[40] rose to a peak after two to three weeks of treatment. The rise was quicker with prednisolone than with cortisone. The peak response of half the children (Cases 86, 5, 78, 25, 23, and 26) rose to within 5% of their predicted normal E.F.R.[40] values at some time during treatment in one or both trials.

Table I shows their assessment without treatment, where the mean E.F.R.[40] values have been expressed as a percentage of the predicted normal to provide an index of abnormality. All these children with chronic asthma had an impaired ventilatory capacity.

## Discussion

We have found that the E.F.R.[40] provides a valuable method of following the progress of patients with

poor ventilatory function due to chronic asthma. In this investigation we have found it useful for assessing the value of different doses of cortisone and prednisolone.

In evaluating the results of this investigation, certain unavoidable difficulties and variables should be kept in mind. Although each child has a reduced ventilatory capacity, even when free from symptoms, many control readings are required to form an adequate baseline in a chronic disease which varies in severity from day to day. An assessment of the severity of the complaint in each child can only be made quantitatively by relating the baseline value with the predicted normal value for the individual. From these two values one can also estimate theoretically the maximal possible response to treatment.

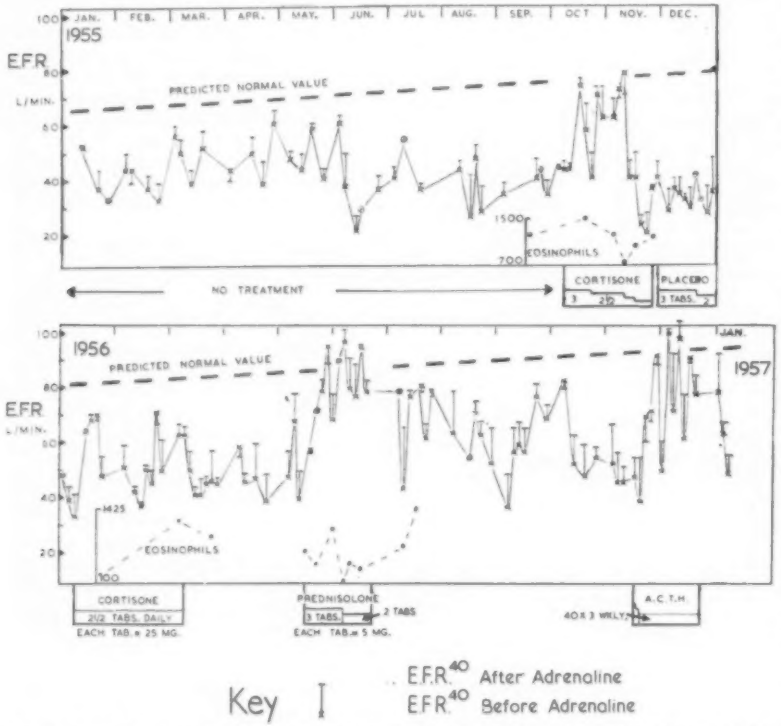


FIG. 3.—Case 78. Graph of E.F.R.[40] readings during 1955, 1956, and the beginning of 1957.

In this paper the therapeutic effects of cortisone and prednisolone are compared. The cortisone trial was carried out 9 to 24 weeks before the prednisolone. To make a valid comparison, therefore, the response to cortisone and to prednisolone had to be assessed using baselines and predicted normal values referable to each course of treatment.

In assessing the results it should also be remembered that prednisolone was given in full doses for a longer time than cortisone.

The data are open to various methods of analysis. One can measure the overall response of the group and of individuals to courses of treatment with cortisone and prednisolone, but this rather crude form of analysis tells one nothing about the response in relation to time and dose. Thus, further analysis of the group and individuals have been made which take these variables into account.

Both cortisone and prednisolone suppress asthmatic symptoms effectively in most cases, and there is little to choose between them in this respect. However, in the 12 cases studied prednisolone rendered two more cases symptom-free than did cortisone on full dosage. Prednisolone has the advantage of not causing salt retention and oedema. Ventilatory capacity is greatly improved by both cortisone and prednisolone. Individuals who responded usually showed a peak response by the second or third week. The response was rather quicker with prednisolone.

Each group had routine E.F.R.[40] readings recorded twice weekly, and the results for each individual were plotted on separate graphs. Analysis of these 12 graphs showed that the full-dosage response was maintained in seven cases on prednisolone and in four cases on cortisone when the dose was reduced. In the remainder, the effect waned as soon as the dose was reduced. Within a week of withdrawing either cortisone or prednisolone, the ventilatory capacity of most of the children deteriorated abruptly. These findings suggest that 75 mg. of cortisone or 15 mg. of prednisolone is a satisfactory daily dose in improving the ventilatory capacity of children with chronic asthma. In many cases these are the minimum doses which will maintain the ventilatory capacity at a near normal level.

In the recent Medical Research Council (1956) trial of the effect of cortisone acetate in chronic asthma the subjects were for the most part adults who received variable doses after an initial loading dose. The disappointing results may well have been due to the maintenance dose being too low. We agree with Savidge and Brockbank (1954) that many cases that do not respond to cortisone may do so on bigger doses.

Favourable reports have been made on the treatment of asthma with prednisolone and prednisone, such as Arbesman and Ehrenreich (1955) and Barach *et al.* (1955). The latter measured the effect of these steroids on the ventilatory capacity; we were also interested to note that they found that prednisone gave a quicker response than cortisone, because we observed that this was also true with prednisolone. The *British Medical Journal* (1957) reviewed the evidence on the activity of prednisone and prednisolone, and concluded that the anti-inflammatory and antirheumatic effect of these new steroids is about equal to that of cortisone, but that weight for weight these new compounds are four to five times more active. From the findings reported here it would appear that the same generalization holds good for the anti-asthmatic effect of these drugs, and that weight for weight prednisolone is at least five times more active than cortisone.

The effect of the adrenaline inhalations during the trials with cortisone and prednisolone was interesting. In our previous communication (Kennedy and Thursby-Pelham, 1956) we observed that the effect of cortisone and adrenaline was additive when the overall group figures were examined. This observation is confirmed in the present report both for cortisone and for prednisolone. From a more detailed study of these results it is seen (Fig. 2) that the response to adrenaline was reduced during the first and second weeks on full dosage, but was enhanced after the third week from starting treatment when the doses of both drugs had been reduced. This increased adrenaline response was most marked in the week or two after cortisone or prednisolone had been withdrawn. We feel that further study is required to explain why, with cortisone and prednisolone therapy, the sensitivity to adrenaline is at first inhibited and later enhanced.

**Summary**

Twelve children with chronic asthma were given a trial course of cortisone and later a trial course of prednisolone, and the results are compared.

The expiratory flow rate (E.F.R.[40]) was used to assess the cases and to measure the response to treatment.

The general effects and relief of symptoms produced by the two drugs were similar, rather more children being rendered symptom-free by prednisolone than by cortisone, on a given dosage.

Seven cases responded better to prednisolone, and two cases responded better to cortisone. The results show that 15 mg. of prednisolone and 75 mg. of cortisone produced a similar satisfactory effect, and on this dosage a peak response was generally observed after two to three weeks. When the dose was reduced, the response usually waned.

The response to adrenaline is at first inhibited and later enhanced during either cortisone or prednisolone therapy.

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# USE OF PRESSOR AGENTS IN SHOCK IN MYOCARDIAL INFARCTION

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The mortality from cardiac infarction, substantially reduced in recent years by the widespread use of anticoagulants, may be capable of still further reduction. There are many patients who develop, at the onset of the attack, a state of shock with low blood pressure. This may be so brief that it has almost passed by the time medical attention is obtained, but when persistent or worsening it has long been recognized as of serious significance. The onset of shock may be delayed for some days, but it is nevertheless of ill omen. When this condition complicates cardiac infarction the mortality rises to about 80% (Selzer, 1952; Gootnick and Knox, 1953; Fink, d'Angio, and Biloon, 1953; Griffith *et al.*, 1954).

Attempts to relieve shock and raise the blood pressure have commonly been unsuccessful, and the wisdom of such attempts has been questioned. Thus plasma and blood transfusions have been ineffective owing to overloading of the circulation and they are now rarely used. The place of digitalis is undecided, although good results have been reported by Gorlin and Robin (1955). Vasopressor drugs used by many investigators have usually been such substances as sympathomimetic amines or their derivatives, including adrenaline, ephedrine, and "paredrine"; all of them produce undesirable effects on the heart itself, such as tachycardia and an increase in the cardiac output and the work of the heart.

The use of pressor agents depends on the assumption that the peripheral vasoconstriction that occurs in the state of shock does not produce a sufficient increase in peripheral resistance. It has been thought that if this peripheral resistance could be further increased a rise of blood pressure would follow and bring about improved circulation to the heart and brain. However, an increase in peripheral resistance alone is not enough to raise the blood pressure; the force of the cardiac contraction itself must be increased in response to the increase in peripheral resistance. It has been found that certain newer amines may possess just such a beneficial direct action on the myocardium. In this paper the results of the use of certain pressor agents in 25 consecutive patients with shock in myocardial infarction are described.

## Pressor Agents

Two compounds have been used in the treatment of these patients. They are L-noradrenaline ("levophed") and mephentermine sulphate ("mephine"). The properties and pharmacological and therapeutic effects of these preparations may be outlined as follows.

*L-Noradrenaline*, the most powerful pressor and general vasoconstrictor agent known, differs from adrenaline in its effects upon the cardiovascular system in some important respects. Unlike adrenaline, L-noradrenaline does not increase the rate or output of the heart. Whereas the total oxygen consumption is raised by 20–30% by adrenaline, it is virtually unaltered by L-noradrenaline. Adrenaline, by its direct effect on the heart, causes a rise in systolic pressure, while the diastolic pressure may fall as a result of the vasodilatation in the large vascular bed of the muscles. L-Noradrenaline, on the other hand, being an overall vasoconstrictor, increases both the systolic and the diastolic pressure. In experiments on dogs Sayen *et al.* (1952) demonstrated that the rise in oxygen tension in the ischaemic zone produced by L-noradrenaline infusion was greater than that caused by inhalation of pure oxygen. Both L-noradrenaline and adrenaline dilate coronary vessels (Burn and Hutcheson, 1949). The pharmacology of L-noradrenaline has been fully reported by von Euler (1955). In fully trained dogs Gazes *et al.* (1953) found that L-noradrenaline increased the contractile force of the heart whereas phenylephrine produced largely pressor effects. They also found that L-noradrenaline gave better results than phenylephrine hydrochloride ("neosynephine") when used to combat shock in patients after myocardial infarction.

*Mephentermine sulphate* has little or no direct action on the heart muscle and causes no alteration in the heart rate or changes in the electrocardiogram. Although the blood pressure rises owing to an increase in peripheral resistance, cardiac output is not significantly altered. In animal experiments (Hellerstein *et al.*, 1952) in which rotameters within the lumen of the vessels were used it was shown that coronary flow increased as the blood pressure rose; the work of the heart increased very slightly, but the cardiac output remained unchanged. If injections were made at too short intervals the response decreased. Mephentermine is metabolized rapidly and there is no danger of cumulative action. The intravenous dosage varies from 10 to 30 mg., and intramuscularly up to 70 mg., while 15 to 30 mg. can be given at half-hour intervals if necessary.

## Method of Use of Pressor Agents

The indication for the use of either of these preparations was simply the existence of shock. While the usual well-

known clinical features of prostration, pallor, sweating, vomiting, coldness of the extremities, and a small thready pulse (not necessarily quick) were present in varying degrees in different cases, the paramount feature of low blood pressure was the one determining the use of L-noradrenaline or mephentermine. If the blood pressure fell below 90 mm. Hg and remained so, particularly if the other signs were impressive, these substances were at once employed. Circumstances particularly calling for their use were abnormalities of rhythm, especially persisting tachycardia, auricular fibrillation, or bradycardia.

If shock was judged to be severe, and if the existing facilities allowed, L-noradrenaline was chosen. It was administered in 5% dextrose or dextrose–saline and not in normal saline, in which it is unstable and deteriorates rapidly. It has been reported by West (1952) that the addition of ascorbic acid to the drip is a further protection against breakdown of the L-noradrenaline, but this substance has not been added to the drip given to any of the patients in the present series. Although skin necrosis did not occur in any of our patients who received L-noradrenaline, it has been reported (Humphreys *et al.*, 1955), and a watch should be kept for a pallor around the vein which would necessitate transferring the drip to an alternative vessel.

An initial concentration of 4 mg. per litre is advised. The drip rate should be adjusted to 60–70 a minute at the start and then doubled after 5 minutes if the blood pressure has not risen by then. The aim should be to maintain a systolic pressure of 100–110 mm. Hg (not more), and the rate of administration of L-noradrenaline should be increased every five minutes, or, alternatively, the concentration doubled until a satisfactory response occurs. Unremitting attention is required both for recording the blood pressure at intervals of two to five minutes and for the frequent adjustments of rate of administration that require to be made in the light of the blood-pressure responses. Cessation of the noradrenaline drip should be slow and cautious.

*Mephentermine* is suitably employed for shock of less severe degree, or when facilities for intravenous infusions do not exist. Its administration is much simpler, usually by intramuscular injections of 15–30 mg. The intravenous route can be used when a more rapid response is desired, the injection being given slowly from a syringe, taking one or two minutes. If the blood pressure fails to rise within five minutes a further 15–30 mg. may be administered in the same manner. As an alternative, 30 mg. may be added to 500 ml. of 5% glucose and given by intravenous drip, the rate being then altered to maintain the desired response. In addition to the use of a pressor agent all shocked patients were treated by anticoagulant therapy in the conventional manner, starting with heparin and phenindione and continuing with the latter alone.

Of the 25 cases of myocardial infarction complicated by shock which form the basis of the present communication, 12 were treated by mephentermine alone, 11 by L-noradrenaline alone, and 2 by both drugs. Six of these cases have already been included in an earlier report (Shirley Smith and Guz, 1953).

## Illustrative Cases

The following seven case reports have been selected as examples of the use and the results of pressor agents in different grades of myocardial infarction with shock of varying degree. In Cases 1 and 2 only L-noradrenaline was used and in Cases 3–5 mephentermine alone. All recovered. The last two cases illustrate the successive use of mephentermine and L-noradrenaline; these patients died in spite of initial response to pressor agents.

### Case 1: Severe Posterior Cardiac Infarction with Left Bundle-branch Block and Profound Shock Treated by L-Noradrenaline Infusion with Recovery

A man aged 49 had a third attack of cardiac infarction on March 19, 1954, with severe retrosternal pain, vomiting, and other evidence of shock. Jugular venous congestion was present and the heart was completely irregular at 150 a minute, the pulse being feeble. Cardiac enlargement and pericarditis were present and the blood pressure was not recordable. The cardiogram showed posterior infarction with left bundle-branch block.

Administration of aminophylline and digoxin intravenously brought no result, but within an hour of the start of intravenous infusion of L-noradrenaline the systolic pressure rose to 120 while at the same time the rhythm became regular at 70 a minute (Fig. 1). Infusion of L-noradrenaline was continued for 11 hours in all, and thereafter the blood pressure was maintained steadily at 120/80. An uneventful recovery ensued.

### Case 2: Septal Infarction Following Anterior Infarction a Year Earlier. Moderate Grade of Shock and Transient A-V Block. Pressor Response to L-Noradrenaline Followed by Recovery

A fishmonger aged 62 was brought to the casualty department on the night of April 30, 1954, after a syncopal attack. He was conscious and complained only of epigastric discomfort. There was no cyanosis, dyspnoea, or sweating. The apex beat was not palpable. The heart sounds were faint and the blood pressure was 75/50. After an hour or two the pulse had fallen to 38 a minute and the blood

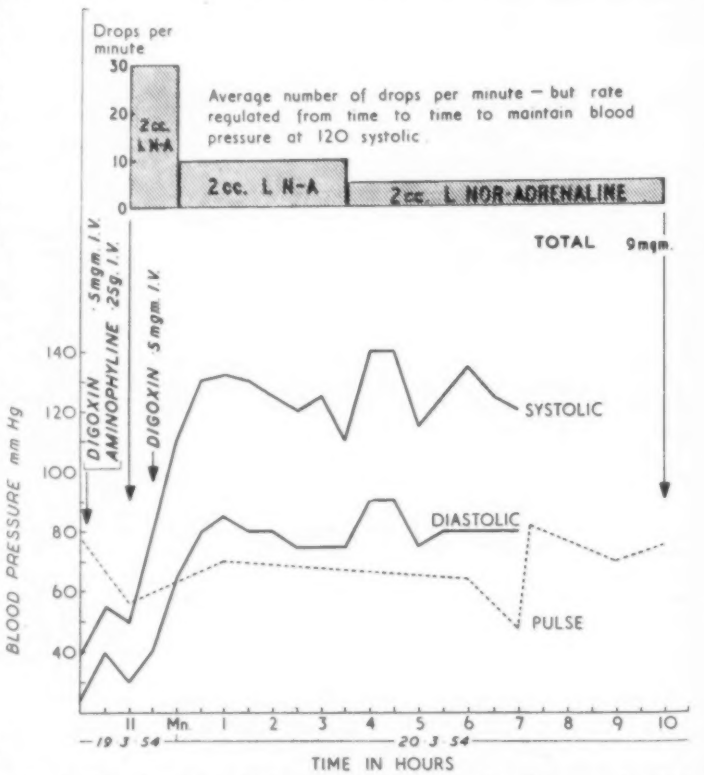


FIG. 1.—Case 1. Severe shock and rapid fibrillation after the onset of a third attack of cardiac infarction. Intravenous infusion of L-noradrenaline was followed at once by restoration of normal pressure and within an hour by conversion to normal rhythm.

pressure to 60/40. Morphine, ¼ gr. (16 mg.), and atropine, 1/100 gr. (0.65 mg.), were given, together with heparin, 12,500 units intramuscularly, and phenindione, 75 mg. An intravenous drip of dextrose–saline containing 4 mg. of L-noradrenaline per litre was begun and run in at approximately 20 drips a minute. Thirty minutes later the blood pressure had risen to 70/50 and the pulse to 50 (Fig. 2). One hour after the start of the infusion the blood pressure had reached 100/70 and the pulse 55. The rate of infusion was therefore reduced to 16 drips a minute. The blood pressure was maintained at a satisfactory level and the pulse rate returned to 66. Nine hours from the start the rate of infusion of L-noradrenaline was further reduced to 10 drops a minute, and after 15 hours, when the blood pressure reached 110/70, it was discontinued.

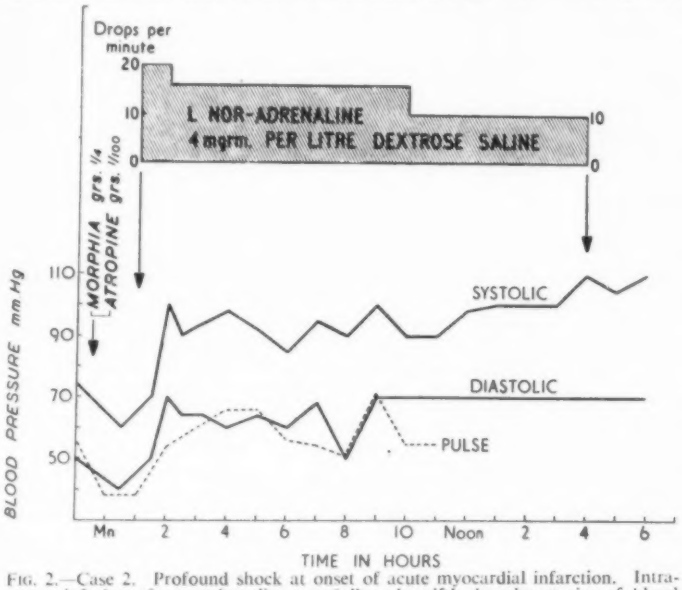


FIG. 2.—Case 2. Profound shock at onset of acute myocardial infarction. Intravenous infusion of L-noradrenaline was followed swiftly by abrupt rise of blood pressure and also by sudden increase in the heart rate.

An electrocardiogram on May 3 showed a recent septal infarction and partial A-V block, but the conduction defect had disappeared in a record taken on May 14. The blood pressure ranged from 70/50 to 100/60. Auricular fibrillation occurred transiently for 10 days during convalescence; he was discharged from hospital on June 20.

**Case 3: Transmural Antero-lateral Infarction Accompanied by Moderate Shock and A-V Block. Good Response to Mephentermine; Recovery**

A research worker aged 54 gave a three-year history of coronary heart disease. On March 30, 1956, he collapsed suddenly with dyspnoea but no pain, and became unconscious briefly. Profuse sweating, pallor, and a blood pressure of 65/40 showed the severe grade of shock. The pulse was regular at 40 a minute. Mephentermine, 30 mg. intramuscularly, was given half an hour after the onset, and this was followed by a rise of blood pressure to 104/70 within half an hour of the injection (Fig. 3). The electrocardiogram showed a transmural antero-lateral infarction of the heart. Gradual recovery followed with signs pointing to aneurysmal bulging of the left ventricle. He was able to return to sedentary work until the time of his sudden death nearly one year after the attack.

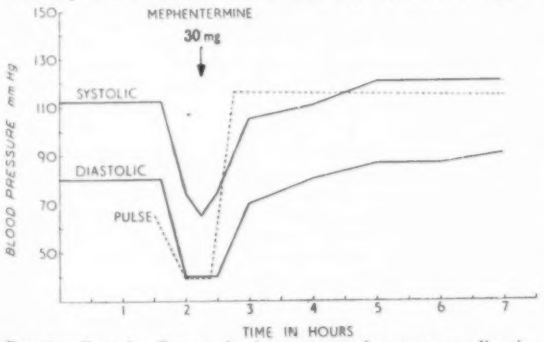


FIG. 3.—Case 3. Severe shock accompanying acute cardiac infarction. The graph shows the immediate rise in blood pressure and pulse rate following intravenous injection of 30 mg. of mephentermine.

**Case 4: Posterior Myocardial Infarction with Moderate Grade of Shock and Transient A-V Block. Treated by Mephentermine with Recovery**

A man aged 45 was admitted to hospital on March 25, 1956, with severe retrosternal pain lasting two hours; there was sweating and nausea and transient loss of consciousness. The pulse was weak at 50 a minute and the systolic pressure was 80; there was no evidence of congestive failure. The electrocardiogram showed transmural posterior infarction with a P–R interval of 0.3 second. In the course of four hours shock had deepened, with cyanosis, increasing pallor, and lethargy; the pulse fell to 40 a minute, and the blood pressure to 70/30. Mephentermine, 30 mg. intravenously, was given during half an hour, after which time the blood pressure had risen to 110/70. Four hours later the pulse was 70 and cyanosis had disappeared. Twenty-four hours later there was a relapse with further retrosternal pain and a renewed fall of pressure to 70/40. The condition was again retrieved by intramuscular and intravenous injections of mephentermine in the same dosage. During the four following days the clinical state fluctuated greatly with a strong tendency to renewal of shock and severe hypotension.

Mephentermine repeatedly showed a specific pressor effect. There was transient auricular fibrillation at the rate of 60 during a period of hypotension. The phase of recurrent shock and hypotension lasted six days. Normal rhythm was established and the latent heart-block completely cleared up, while the blood pressure remained consistently at 110 systolic during convalescence.

**Case 5: Postero-lateral Infarction in a Hypertensive Patient. Delayed Shock of Moderate Grade Responded to Mephentermine. Recovery**

A housewife aged 59 with hypertension and coronary disorders had been under treatment for three years. On June 27, 1956, she had severe enduring substernal pain with some evidence of shock. The electrocardiogram showed a large postero-lateral cardiac infarction; the heart was enlarged and gallop rhythm was present. The blood pressure was 170/90. Nineteen hours after the onset further severe pain developed and the blood pressure fell to 90/60. The hypotension was relieved by the intramuscular injection of mephentermine, 15 mg. (Fig. 4). The chart shows subsequent temporary fall of pressure not sufficient to require further pressor treatment. However, three days after the onset there was a further dangerous relapse with the pressure falling to 90/40; this was speedily relieved by further injections of mephentermine, and the patient went on to make a full recovery.

**Case 6: Anterior Myocardial Infarction. Severe Shock Failed to Respond to Mephentermine and L-Noradrenaline. Death Ensued**

A housewife aged 52 had had angina of effort for five years. Sympathectomy had been performed for hypertension in 1950. She was admitted to hospital on March 1,

1956, with severe gripping retrosternal pain of six hours' duration, vomiting, and sweating. The rhythm was regular at 70 a minute, and the blood pressure was 90/60. An injection of morphine was given and anticoagulant treatment was started. Mephentermine, 30 mg., was given by intramuscular injection. As no improvement was evident an hour

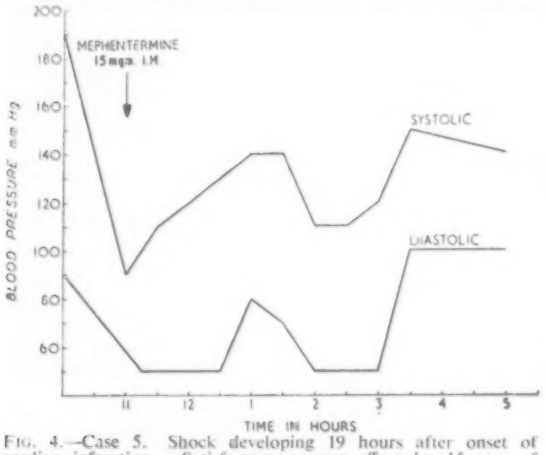


FIG. 4.—Case 5. Shock developing 19 hours after onset of cardiac infarction. Satisfactory pressor effect by 15 mg. of mephentermine given intravenously.

and a half later this dose was repeated, intravenous injection having failed. Nevertheless the pulse rate increased to 160 and the blood pressure remained unaltered with deepening shock and signs of venous congestion developing. In spite of intravenous infusion of L-noradrenaline the blood pressure became unrecordable and remained so until her death six hours later. Necropsy showed thrombosis of the descending branch of the left coronary artery.

**Case 7: Extensive Transmural Infarction Postero-laterally in Left Ventricle and a Smaller Infarct Anteriorly. Severe Shock with Congestive Heart Failure. Initial Response to Mephentermine not Maintained, and no Pressor Response to L-Noradrenaline. Death within 24 Hours**

A man aged 55 had a five-year history of retrosternal pains radiating to the interscapular region, occurring always 10 minutes after exertion, never during effort. Ten days before admission he was awakened by severe angina, spreading on this occasion to the arms; it persisted for nine hours, accompanied by sweating and nausea. Weakness but no dyspnoea followed the attack. On admission to hospital on February 18, 1956, he was ill and feverish and the pulse was small though regular. The blood pressure was 130/100. There were signs of cardiac enlargement and raised jugular venous pressure with bilateral pulmonary oedema. All peripheral pulses were palpable.

Treatment was started by heparin and phenindione and oral digoxin. On the day after admission he collapsed suddenly with profuse sweating and an unrecordable blood pressure. Mephentermine, 30 mg. intravenously, was given. The blood pressure rose to 125/100, but within three hours had again become unrecordable, with the pulse rate rising to 110. Deepening shock with vomiting and sweating was treated by a further 30 mg. of mephentermine intramuscularly, but in spite of this and the simultaneous starting of infusion of L-noradrenaline death took place half an hour later.

Necropsy showed the heart weight to be 530 g. with hypertrophy of the left ventricle. Transmural infarction was found in the posterior wall of the left ventricle, and the lesion involved the whole of the septum and part of the anterior wall of the left ventricle. Recent thrombosis was present in the anterior descending branch of the left coronary artery and also in the right coronary artery, these vessels being diffusely involved in severe non-calcifying atheroma.

## Results and Discussion

Shock due to cardiac infarction differs from surgical shock in certain fundamental respects not yet fully understood. Whereas in surgical shock the heart is healthy and the condition is explained by a diminution of effective circulating blood volume, in myocardial infarction the heart has suffered more or less severe damage and there is no reduction of the circulating blood volume (Boyer, 1944). The initiating factor is the heart itself, the output (mainly of the left ventricle) being reduced owing to a loss of functioning myocardium. Freis *et al.* (1952) found the cardiac output and stroke volume to be reduced, while total peripheral resistance, central venous pressure, and heart rate were increased. The systemic and pulmonary blood volumes were unaltered. However, it has also been found that in some instances there is a widespread vasodilatation in the muscle vascular bed which in the presence of a normal cardiac output results in a fall in blood pressure.

The diminution of coronary blood flow which occurs in shock following myocardial infarction (Corday *et al.*, 1949) impairs further the efficiency of the uninfarcted myocardium and aids in the establishment of a vicious circle whereby low blood pressure reduces coronary flow which still further impairs myocardial contractility, decreasing the stroke volume and the output of the heart. Peripheral vasoconstriction may then occur in an effort to raise the blood pressure sufficiently to improve coronary flow and so halt the process. It is possible that when this does not come about the use of such pressor agents as are here described furthers a process already initiated by the body. To these mechanisms may be added a prolonged circulation time, pulmonary congestion, and a raised venous pressure due to heart failure.

A fundamental fault lies, therefore, in the myocardium. It is important to use a pressor agent whose action does not depend solely on increasing peripheral resistance, for it has been shown that in the presence of a damaged myocardium an increase in peripheral resistance only diminishes still further the cardiac output (Sarnoff *et al.*, 1954). Both mephentermine and L-noradrenaline act directly upon the myocardium to restore the cardiac output; thus with the aid of an increase in peripheral resistance they produce a sustained improvement in the circulation by establishing a satisfactory level of blood pressure.

In the present series of 25 consecutive patients, 12 died. This figure compares favourably with the average mortality of 80% given by most workers for patients who did not receive pressor agents as part of their treatment. On considering the clinical features of our cases certain features emerge for comment.

*Previous Cardiac Infarction.*—As might be expected, a history of such weighed against recovery. Six of the 12 fatal cases gave a history of previous infarction as compared with three of the survivors.

*Duration of shock* prior to the institution of treatment often determined the outcome. The average duration of shock in those who survived was 1 hour 40 minutes as compared with five hours in the fatal cases. Gootnick and Knox (1953) concluded that the duration of hypotension was important and that irreversible shock developed during periods of prolonged hypotension; of their 32 cases of severe post-infarction shock, none survived when hypotension persisted over eight hours. Sampson and Zipser (1954) also recorded that duration of shock in their patients who died was twice as long as in those who survived. In the series reported by Griffith *et al.* (1954) 13% of those who had pressor treatment within three hours died, whereas among those in whom shock had existed more than three hours 76% died.

*Overfilling of Jugular Veins.*—The appraisal of the cervical veins is not easy in shocked patients and time was not spent in making intravenous recordings. However, if the cervical veins were conspicuous other evidence of heart failure was generally present. A raised jugular venous

pressure was found in 8 of the 12 patients who died, but in only 4 of the 13 who recovered. The coexistence of heart failure worsened the outlook for the shocked patient.

*Persistent tachycardia* was an unreliable guide to prognosis although in general it was unfavourable. It occurred in nine of the fatal cases, but also in six of those who survived.

*Bradycardia* resulting from partial A-V block occurred in 25% of survivors, but was not seen in those who died. Its occurrence is of limited value, but may perhaps point to a likelihood of recovery. The slow ventricular rate, by allowing both more time for coronary filling during diastole and for myocardial recovery, may conceivably be of benefit to the heart during this critical phase. A-V block may be functional and due to temporary anoxia of the conducting tissue and not to septal infarction. Such functional impairment of conduction has been reported by Lewis *et al.* (1914), who showed how experimentally induced anoxia in cats caused interference with conduction, and they demonstrated that it is the A-V node and the tissues immediately above that are the most susceptible to oxygen lack. In man Greene and Gilbert (1921) showed how a progressive lack of oxygen induces a series of changes in cardiac rhythm and conduction of impulse from auricle to ventricle.

*Grade of Pressor Response.*—The height to which the blood pressure rises in response to the use of pressor agents is not a reliable guide to whether or not any individual patient is likely to survive. The average rise in blood pressure after the use of one or other pressor agent, or in some cases of both, was 42/33 in those who ultimately succumbed, and 59/35 in those who survived. This lack of relationship was seen in one of the fatal cases, in which the blood pressure rose from an unrecordable level to 125/100 following the administration of mephentermine, while two surviving cases showed rises of only 35/20 (from 60/40 to 95/60 and from 80/60 to 115/80). The most that can be learned from the response is that the higher the rise in diastolic pressure the more likely is the patient to survive, for it is only when an effective diastolic pressure is maintained that adequate coronary circulation is assured to the surviving myocardium.

### Prognosis after Recovery from Shock

It has sometimes been held that pressor treatment in the shock of myocardial infarction is of little ultimate value because the remote prognosis remains, in any case, very poor. This is by no means a valid objection, as is shown by the follow-up of those cases previously reported jointly by one of us (Shirley Smith and Guz, 1953). Of their six patients, three survived and were still alive nearly four years after sustaining their original infarction complicated by grave shock.

Two of these have been re-examined and news has been received of the third. Case 2 of the series, aged 71, whose infarction occurred shortly after a major operation in September, 1952, was seen in November, 1956, when she was well and free from pain. Her activity was restricted by osteoarthritis of the hip, but she was not short of breath and showed no signs of failure. The blood pressure was 130/80.

Case 3 of the series, aged 57, had a myocardial infarction in May, 1953. At review in August, 1956, he complained that only in the last four months had he developed some angina on effort and increasing dyspnoea. No signs of heart failure were present. The blood pressure was 140/90.

Case 5 of the series, aged 75, was treated with L-noradrenaline infusion for five hours in April, 1953, when in shock after myocardial infarction. It has not been possible to re-examine this patient, but in March, 1957, her sister wrote to say that she has remained in satisfactory health ever since. Her medical attendant has died, but she has had no occasion to consult his successor.

### Summary

The purpose of the present report is to draw attention to the place of pressor agents in the treatment of shock complicating myocardial infarction. Hitherto myocardial infarction accompanied by severe shock has carried a mortality of 80%. In our consecutive series of 25 cases, only 12 have died. We hold that by the early recognition of the presence of shock and its prompt treatment a number of patients can be saved. That the survivors can lead useful lives free from serious disability for several years is shown by the follow-up of the survivors of the series published by one of us nearly four years ago.

The pressor agents used were L-noradrenaline by intravenous drip infusion, and mephentermine, both intramuscularly and intravenously. Initial treatment of lesser grades of shock should be by intramuscular mephentermine; L-noradrenaline should be used for severe shock and in less severe illness when mephentermine has not been effective. Whereas mephentermine is readily administered as emergency treatment when the patient is first seen, L-noradrenaline requires careful attention to its continuous intravenous administration, thus generally necessitating admission of the patient to hospital.

The duration of shock before treatment is started should be less than two hours if a good result is to be obtained. When shock has been present more than five hours the results of treatment are poor. A raised jugular venous pressure, a history of previous infarction, and a persistent tachycardia are all of ill omen.

An unexpected finding in our series was that bradycardia, even if due to functional A-V block, seemed to indicate a good prognosis.

We are indebted to Dr. F. G. Hobson for clinical details relating to Case 1 and for permission to include these in the present publication.

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"Ergot—the Story of a Parasitic Fungus" is the title of a new film made by the Wellcome Foundation Film Unit. Sir Henry Dale O.M. and Professor Chassar Moir helped with the making of the film, the latter appearing in it to describe the discovery of ergometrine in 1935. The film tells the story of ergot as both a toxic contaminant of rye bread and a valuable medicinal substance. It describes how the complex alkaloids of ergot were isolated and the use to which they are now being put in the treatment of disease and the management of childbirth. Some of the sequences were shot with the help of the obstetric unit of University College Hospital, London. The film (16 mm., colour, with sound track) runs for 27 minutes, and can be borrowed from the Wellcome Film Library, The Wellcome Building, Euston Road, London, N.W.1, free of charge.

# ANTICOAGULANTS IN MYOCARDIAL INFARCTION

BY

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The use of anticoagulants in the treatment of myocardial infarction has greatly increased in recent years, and practically all reports have acknowledged their value. It has usually been accepted that anticoagulant therapy reduces the mortality rate in myocardial infarction by as much as a third or a half. The only serious argument in recent times about the value of anticoagulants has been whether these drugs should be used in so-called "good-risk" cases as opposed to "bad-risk" cases. Russek and Zohman (1957) define bad-risk patients as those with a history of previous infarction, who have intractable pain, extreme or persistent shock, significant cardiac enlargement, arrhythmia, or diabetic acidosis.

Russek and Zohman have been the principal proponents for the limited use of anticoagulants—that is, for giving anticoagulants to bad-risk patients only. They have shown that the mortality rate in good-risk patients, even without the use of these drugs, is very low—3.3% in a review of 1,000 cases (Russek and Zohman, 1957)—and they therefore consider that the value of anticoagulant therapy for these patients is questionable, especially as the use of anticoagulants is not without risk. Wright (1957) and many other authorities, whilst agreeing that good-risk cases have a low mortality, believe that these cases can be determined only in retrospect—that is, good-risk patients often rapidly become bad-risk patients—and therefore they advise the use of anticoagulants for all patients with cardiac infarction, unless there is some special contraindication to their use.

Russek and Zohman, whilst denying the value of the routine use of anticoagulants for good-risk patients, state that "the value of anticoagulants in properly selected patients—those with poor prognostic signs—constitutes a major advance in the treatment of acute myocardial infarction." Therefore, in view of the widely accepted opinion of the value of anticoagulants, at least for all bad-risk patients, the report by Honey and Truelove (1957) is most surprising. These authors state that the use of anticoagulants at the Radcliffe Infirmary at Oxford has not made a dramatic difference to the mortality rate in cardiac infarction, and that anticoagulants have saved lives solely by abolishing the risk of pulmonary embolism.

Honey and Truelove show in their detailed analysis of patients with myocardial infarction admitted to the Radcliffe Infirmary that there appeared to be a definite bias in the selection of patients for treatment with anticoagulants, and that a high proportion of bad-risk patients were not treated. At New End Hospital I have for many years considered the diagnosis of myocardial infarction to be a specific indication for the use of anticoagulants and have for some time been of the opinion that there is very seldom any contraindication. I believe, therefore, that it is of value to compare in detail the results of Honey and Truelove's series with mine, and that the effect of this comparison is to render their conclusion that anticoagulants are of little value in the treatment of myocardial infarction questionable. This comparison is perhaps of particular importance in view of the editorial comments in the *Lancet* (1957) supporting the views given as a result of the review of cases treated at the Radcliffe Infirmary.

## Sources of Data

All patients in the New End series were under my care and were admitted to hospital between 1951 and 1957. In all cases the diagnosis was confirmed by electrocardiograph or at necropsy. Honey and Truelove, in reviewing their 543 admissions, state that no fewer than 75 out of the total 195 deaths (38%) occurred in the first 48 hours after admission. They say: "This reflects the fact that the Radcliffe Infirmary receives a large proportion of its patients as acute emergencies soon after the actual infarction. (The results obtained in different hospitals are difficult to compare because of differences in the proportion of patients admitted in the earliest and most dangerous stage of the disease.)"

Between 1951 and 1957, 326 patients with proved myocardial infarction were treated with anticoagulants at New End Hospital. In this group there were 67 deaths. The early deaths in the first 48 hours were 26 (38%), which is the same as at the Radcliffe Infirmary. However, to show how severely and seriously ill the patients admitted to New End Hospital are, I should add that there were in this period a further 52 patients admitted with infarction, all of whom died within 24 hours and of whom all but a few died within a few hours of admission—that is, too soon for a definite diagnosis to be established and for the patient to receive anticoagulant therapy. Therefore 65% of the deaths at New End Hospital in the period under review occurred in the first 48 hours—that is, nearly twice as high a percentage as in the Radcliffe series. Not one patient was denied treatment because of any specific contraindication. This, I believe, rules out any question of bias in the selection of patients for treatment.

*Age Comparison.*—Honey and Truelove rightly demonstrate the well-known fact that in each sex the fatality rate increases with advancing years. Table I shows the composition in terms of age of the Radcliffe and New End series. It is seen that the New End series contains a higher proportion of patients in the older age groups. In the 70- and 80-year-old group, in which the mortality in untreated patients is particularly high (from 50 to 80%), the percentage of patients in the New End series is 30.9% compared with 24.6% in the Radcliffe series.

TABLE I

| Age in Years | No. of Patients | |
|---|---|---|
| | New End | Radcliffe |
| <40 | 8 | 10 |
| 40— | 37 | 71 |
| 50— | 69 | 149 |
| 60— | 111 | 179 |
| 70— | 80 | 115 |
| 80+ | 21 | 19 |
| | 326 | 543 |

### Comparison of Factors Affecting Prognosis in the Acute Attack

Before we can try to compare the results of anticoagulant therapy in the New End series of 326 treated cases and the Radcliffe group of *110 untreated cases* it is essential, as Honey and Truelove state, that the various factors affecting prognosis be carefully compared in both groups—that is, that the proportion of good- and bad-risk cases in each group be carefully taken into account.

The percentage of good-risk patients in the untreated group of 110 patients in the Radcliffe series was 24.5%, while in the New End series it was 25.7%.

In assessing the various factors associated with a bad late prognosis so as to compare the Radcliffe and New End series, I have included in the bad-risk group only those patients with definite unequivocal signs related to a poor prognosis as mentioned by Honey and Truelove. I have

already shown that there is a very high proportion of patients in the earliest and most dangerous stage of the disease admitted to New End, with a rate of early deaths to late deaths nearly twice as great as in the Radcliffe series. The age composition of the two series is seen in Table I. Finally, Table II shows the proportion of patients with cardiac

TABLE II

| | New End | | Radcliffe | |
|---|---|---|---|---|
| | No. of Patients | % | No. of Patients | % |
| Heart failure | 114 | 38 | 143 | 30·5 |
| Arrhythmia | 107 | 35·6 | 83 | 17·7 |
| Shock and hypotension | 35 | 10·7 | 41 | 7·7 |
| Shock or hypotension | 78 | 24 | 71 | 13 |

failure, arrhythmia, shock, and hypotension in both series. It can be seen that the percentage of patients with heart failure is much higher in the New End group—38% as compared with 30.5% in the Radcliffe group. Similarly the percentage of patients with arrhythmia in the New End series was considerably greater—35.6% compared with 17.7%.

If all the factors mentioned by Honey and Truelove in assessing good- and bad-risk patients are taken into account a valid comparison may be made between the Radcliffe and New End series, bearing in mind that all patients in the New End series were treated and that there was no bias in the selection of the patients. The late mortality rate—that is, excluding deaths in the first 48 hours—in the Radcliffe series of 110 untreated cases was 28.3%, while in the New End series it was only 13.6% (Table III). The expected mortality

TABLE III

| | New End | Radcliffe |
|---|---|---|
| Total No. of patients | 326 (treated) | 110 (untreated) |
| Early deaths in first 48 hours | 26 | 18 |
| Late deaths | 41 | 26 |
| Late mortality rate | 13·6% | 28·3% |
| Good-risk patients | 25·7% | 24·5% |

rate of the New End series, based on Honey and Truelove's calculations, was 27.8%, taking into account that the percentage of good-risk patients was 25.7%.

These results do not bear out the conclusion of Honey and Truelove that anticoagulants have little effect in reducing the mortality rate in acute myocardial infarction. The results shown here, where the expected death rate is reduced by half, is in keeping with most published results from authorities experienced in the use of anticoagulant therapy.

## Control of Anticoagulant Therapy

The control of anticoagulant therapy, even to-day, with all the experience gained over many years, is not simple. For proper control it is essential for the clinician to be fully experienced in the use of anticoagulant drugs and to be conversant with the laboratory procedures. Only good team-work can achieve the best results: by best results is meant not only the avoidance of haemorrhage but, just as important, the achievement of an adequate therapeutic cover. In order to avoid the danger of haemorrhage the importance of maintaining adequate anticoagulant therapy throughout the illness is often overlooked.

Adequate laboratory control is essential for the proper maintenance of anticoagulant therapy. Perhaps the greatest single factor in effective laboratory control is the preparation of an active and reliable thromboplastin which gives constant times with normal control plasma. Quick's prothrombin time, using a reliable thromboplastin, has stood the test of time and gives very reliable results. However, with the simultaneous use of Quick's, Owren's (Owren and Aas, 1951), and Ware's modification of Owren's technique (Ware and Stragnell, 1952) in over 2,000 estimations for in-patient therapy, I have found Owren's method superior to the others (Toohey, 1958).

## Choice of Anticoagulant Drug

If it is accepted that anticoagulant therapy is of value, then the more quickly an adequate anticoagulant cover is provided the better. For this reason, ideally, all patients treated with anticoagulants should be given heparin for the first 24 hours or longer, according to the type of coumarin compound also used.

There are many different coumarin-type anticoagulants available, and it has been truly said that the anticoagulant of choice is the drug that you are most familiar with. To achieve the best results with anticoagulants is not mainly, or even primarily, a question of Quick's technique versus Owren's; given adequate laboratory control, with either Quick's or Owren's method, the most important factor is an experienced clinician who prescribes a drug he is familiar with and who understands the basic essentials of laboratory control.

Because of their slow, prolonged cumulative action, which may take days to appear, the longer-acting coumarin derivatives are undoubtedly more difficult to control than the quick-acting drugs. The latter have the advantage that any change in the maintenance dose is quickly reflected in the prothrombin estimation. Because any change in dose or sign of incorrect dosage is rapidly reflected in the blood estimation, quick-acting coumarin drugs are far easier to use and the correct maintenance dose of the anticoagulant is more quickly arrived at. The quick-acting coumarin derivatives commonly used are phenindione ("dindevan") and ethyl biscoumacetate ("tromexan"). In my opinion the latter drug has too short-lived an effect, with the result that it is difficult to maintain adequate anticoagulant cover with it. Phenindione is a comparatively easy drug to control, and in my experience is one of the best drugs as yet available. The incidence of agranulocytosis with this drug is low, considering its widespread use, and should never prevent its use. The incidence of drug rashes with phenindione is about 1 to 2%; again it will be found that more often than not, when a rash develops, other drugs, especially barbiturates, are also being given.

The longer-acting anticoagulants available, such as phenylpropylhydroxycoumarin ("marcoumar"), diphenindione ("dipaxin"), and dicoumarol, are, I have found, less satisfactory to use than phenindione. Recently there have been reports that warfarin sodium ("coumadin") is the "anticoagulant of choice." This anticoagulant is very nearly as quick-acting as phenindione, but has a more cumulative effect. Because of its rapid action any change in dose is quickly reflected in the prothrombin estimation, and so the necessary adjustment in the dosage can be quickly made.

Table IV shows my results with different anticoagulants. Whether the number of patients treated with each drug is statistically significant, thus enabling any definite conclusion

TABLE IV

| Anticoagulant | Patients Treated | Late Mortality Rate |
|---|---|---|
| Phenindione | 71 | 8·4% |
| Phenylpropyl-hydroxycoumarin | 94 | 21·2% |
| Diphenindione | 73 | 12·3% |
| Warfarin sodium | 35 | 14·2% |

about their relative merits to be arrived at, is perhaps open to question. It should be noted that the number of patients treated with warfarin sodium is certainly too small to mean much.

Before leaving this question of choice of anticoagulant it is essential to point out that the above remarks apply to treatment for an acute illness where it is important to achieve and maintain an adequate anticoagulant cover as quickly as possible. For long-term prophylactic treatment the whole problem is entirely different, and long-acting coumarin derivatives such as marcoumar are, if anything, better than the quick-acting drugs. My experience of over 130 patients on long-term anticoagulant therapy has proved marcoumar

to be an ideal drug for this purpose. The control of long-term anticoagulant therapy presents many different problems from those of short-term therapy for the acute illness.

### Haemorrhage in Anticoagulant Therapy and the Use of Vitamin $K_1$

In my opinion the danger of haemorrhage has been exaggerated. The occurrence of minor haemorrhage, such as slight epistaxis, is not uncommon when adequate anticoagulant therapy is being given. Such minor episodes do not call for cessation of treatment, but merely for a regulation of the dose of anticoagulant where necessary.

Vitamin $K_1$ is one of the most powerful drugs in use, and, while it is invaluable in anticoagulant control, it must be used with the greatest possible caution. It should be given only if there are very definite indications for its use. Briefly its use falls into two main categories: first, to reduce a very prolonged prothrombin time even where there is no evidence of haemorrhage; and, secondly, when more than minimal haemorrhage has occurred. For the first only very small doses of vitamin $K_1$ are needed, such as 2 to 3 mg., and rarely is an initial dose as large as 5 mg. required. If larger doses are given the patient may escape from anticoagulant cover with a resultant very definite risk of fresh thrombo-embolic episodes. If the first small dose does not have the desired effect the same amount should be repeated after 12 hours.

If severe haemorrhage has occurred larger doses of vitamin $K_1$ will be necessary, such as 10 to 20 mg. It should be realized that 10 mg. is a large dose, while it is certainly seldom necessary to give more than 20 mg. It is better, subject to the urgency of each individual case, to give small repeated doses at intervals of 8 or 12 hours, and to regulate the dosage by repeated 8- or 12-hourly prothrombin estimations, than to give a large initial dose and render the patient refractory to anticoagulants.

*Use of Other Drugs with Anticoagulants.*—In prescribing anticoagulant therapy particular care must be taken if oral antibiotics such as penicillin, and especially the broad-spectrum tetracycline antibiotics, are given at the same time. Oral antibiotics enhance the action of oral anticoagulants, and the dose of the anticoagulant will therefore probably have to be reduced. Phenylbutazone ("butazolidin") is known to cause haematemesis, and should never be used together with anticoagulants. Similarly, aspirin is well known for its irritant effect on the gastric mucosa and has often caused haematemesis. Aspirin and all aspirin-containing remedies must never be given to patients on anticoagulant drugs, as haemorrhage is very likely to occur. Again, large doses of salicylates, and probably quinine, reduce the prothrombin level and thus potentiate the effect of anticoagulants. Lastly, it is an impression of mine that frequent doses of liquid paraffin or similar oil emulsions interfere with the absorption of oral anticoagulants, and I therefore avoid their use.

### Anticoagulants for All

There is little doubt, to my mind, that anticoagulants are a major advance in the treatment of the bad-risk patient with myocardial infarction. Even Russek and Zohman, the most severe critics of anticoagulant therapy, agree that all bad-risk patients must be treated. The problem remains whether good-risk patients should be given anticoagulants, as the mortality rate for such patients is so low: Russek and Zohman (1957) estimate 3.3% in a series of 1,000 good-risk patients. In my total series of 326 patients there were only 3 deaths among 84 good-risk patients—that is, 3.5%. With such a low mortality rate I believe that there is room for the opinion that such patients need not have anticoagulant therapy, and I certainly believe that unless skilled clinical as well as laboratory control is available it is better not to use anticoagulants for good-risk patients. With skilled clinical and laboratory facilities available, however, there is nothing to lose in giving anticoagulants, especially as there is always the problem of satisfactorily classifying patients as good- or bad-risk patients at the time they are first seen. Of the 326 patients in this series, 12 initially classified as good-risk changed to bad-risk patients in a short period of time.

With adequate facilities at hand it is exceptional for a patient needing anticoagulant therapy to be denied such treatment. In the last five years at New End Hospital not one patient has been considered to have an absolute contraindication for anticoagulant therapy. Major surgical procedures, including intestinal surgery, have been performed while patients have continued to have anticoagulant treatment. Such minor procedures as dental extractions have been commonplace with patients on long-term treatment without the need for cessation of anticoagulant therapy.

### Conclusions

As a result of an analysis of patients admitted to the Radcliffe Infirmary, Honey and Truelove recently came to the conclusion that anticoagulants are of but little value in the treatment of acute myocardial infarction. They state that in comparing treated and untreated patients it is essential to take into account the number of bad-risk patients, and the age grouping in each series.

A series of 326 patients treated at New End Hospital from 1951 to 1957 have been strictly classified according to all the bad-risk factors mentioned by Honey and Truelove, and the age groups are given to show that this series is in every way comparable to that of Honey and Truelove. In their group of 110 untreated patients there were 24.5% good-risk patients, and the mortality rate, excluding deaths in the first 48 hours, was 28.3%. In the New End series of treated patients the number of good-risk patients was 25.7%, but the mortality rate was only 13.6%. In other words, the death rate was about half. These findings confirm the view, widely accepted by most authorities experienced in the use of anticoagulants, that anticoagulants are of real value in the treatment of acute myocardial infarction.

In my opinion all bad-risk patients should be treated with anticoagulant therapy. In assessing bad-risk factors I agree fully with the criteria laid down by Russek and Zohman—previous history of infarction, intractable pain, cardiac failure, arrhythmia, significant cardiac enlargement, diabetic acidosis, and severe shock and hypotension.

The control of anticoagulant therapy calls for considerable skill, not only to avoid haemorrhage, but, just as important, to give effective anticoagulant cover throughout the whole course of the illness. In the control of treatment there are two equally important essentials—adequate laboratory technique and administration of the anticoagulant drug by a clinician experienced in its use.

In carrying out reliable laboratory control perhaps the most important factor is the availability of an active and potent thromboplastin which gives uniform results from day to day. Better laboratory techniques, such as Owren's as opposed to Quick's method, will, however, be completely offset by inexperienced prescribing of the anticoagulant drug. For adequate anticoagulant therapy the clinician must be thoroughly familiar with the anticoagulant used. For short-term treatment of the acute illness, as opposed to long-term preventive treatment, the quick-acting coumarin drugs such as phenindione and warfarin sodium are much easier to control than long-acting drugs such as dicoumarol and marcoumar. (For long-term therapy the opposite holds true.)

With experienced control serious haemorrhage is very rare nowadays, and minor haemorrhage, though not infrequently seen with adequate therapy, does not call for cessation of treatment. Vitamin $K_1$ is invaluable in the control of haemorrhage due to overdosage with anticoagulant drugs, but it must be used with caution, and in very small doses, as it is so potent.

Certain drugs enhance the effect of oral anticoagulants or may cause haemorrhage. As a result, the administration of oral antibiotics, particularly the broad-spectrum drugs such as the tetracyclines and to a less extent penicillin, may call for a reduction in the dose of the anticoagulant drug. Aspirin, phenylbutazone, and probably quinine should not be given at the same time as anticoagulant therapy, and liquid paraffin is also best avoided.

With skilled laboratory and clinical control, emergency surgical procedures, including major operations, can be carried out on patients still receiving adequate anticoagulant cover without the necessity for the treatment to be stopped altogether. This is particularly important in relation to long-term therapy.

In experienced hands anticoagulant therapy has proved so beneficial in thrombo-embolic disorders that everything possible should be done to ensure that the treatment is carried out to the best advantage and that adequate anticoagulant cover is maintained throughout the illness. To-day, with the increasing use of long-term anticoagulant therapy, there is perhaps justification for a special unit in large hospitals for the control of this treatment.

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# A TECHNIQUE FOR INVESTIGATING THE BLOOD SUPPLY OF MUSCLE DURING EXERCISE

BY

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One of the major difficulties in investigating problems of diagnosis and treatment in intermittent claudication has been the lack of a suitable objective test for measuring blood flow in the calf muscles during exercise. Plethysmographic studies of muscle are relatively easy to perform with the patient at rest, but such investigations do not help in patients with claudication, because resting blood flow is usually adequate. It is only when exercise leads to a demand for blood greatly above the resting flow that claudication is manifest, and during exercise plethysmography is extremely difficult to perform.

The test described in this paper is based on experimental work carried out over the last few years and has been in use by this clinic for four years, some 200 patients having been investigated. As in the case of any test, it is essential to appreciate the basic factors concerned and to be aware of the limitations of the method. It is proposed in this paper to describe the technique which has been evolved and to discuss the interpretation of the results obtained in the light of experimental findings.

In 1948 Kety published a paper reporting the measurement of the local clearance of radioactive sodium previously injected into a tissue, and suggested that this might prove to be a method for the experimental study of the peripheral circulation. As a result of an investigation of the clearance of injected radioactive sodium from muscle it was established (Walder, 1955) that with certain provisos *changes* in the clearance rate were linearly related to *changes* in blood flow (Fig. 1). The clearance rate of radioactive sodium is expressed as the "clearance constant" K.

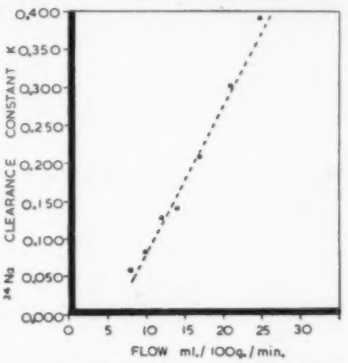


FIG. 1.—Relationship between blood flow as measured with a conventional type of plethysmograph and radioactive sodium clearance constant K in the human gastrocnemius muscle during the immediate post-exercise period.

$$K = \frac{\log C_1 - C_2}{0.4343\ (t_1 - t_2)}$$

where $C_1$ and $C_2$ are the percentage activity of the injected $^{24}$Na remaining at the two times $t_1$ and $t_2$ after the first measure of activity, which is taken as 100%. Hence, by calibration of clearance rate against blood flow measured at rest, the method can be developed in such a way that it becomes easy to measure blood flow during exercise.

While the problems of measuring blood flow in muscle during exercise were being investigated it was noticed that in the case of patients suffering from peripheral vascular disease the $^{24}$Na clearance curve during the type of exercise used showed a characteristic pattern such that there appeared to be *no* flow through the muscle during the period of exercise. This observation allowed considerable simplification of the clinical test for vascular sufficiency during exercise to be made, since it is only changes in blood flow that are required and it becomes unnecessary to measure the absolute blood flow at any stage of the test.

### Object of the Test

The object of the test is to detect vascular insufficiency in human muscle. It allows such insufficiency to be demonstrated at a very early stage in its development, and in those instances where patients describe symptoms which may or may not be attributable to muscle ischaemia during exercise the test enables a firm decision to be made one way or the other. Since any one muscle can be selected for testing it enables the exact location of the ischaemic muscle to be determined, a point which opens up the possibility of performing localized neurectomies as treatment for some cases of claudication. Finally, provided that the test is performed under properly controlled conditions, it offers objective evidence of the state of the circulation in a muscle and a record which can be used for comparison later with subsequent tests following treatment. This latter point is of importance in that it provides an objective means of assessing the results of treatment for a condition where the patient's desire to be better and the doctor's enthusiasm can so colour the picture.

### Technique of the Test

In its simplest form the apparatus for the test consists of an end-window geiger counter tube (Type GM4) mounted in a simple sorbo rubber strap (Fig. 2) and a ratemeter (Fig. 3).

An injection of 0.2 ml. of radioactive isotonic NaCl containing approximately 20 $\mu$C of $^{24}$Na is made through a 26-gauge 2-in. (5-cm.)-long hypodermic needle into the belly of the muscle to be tested. The GM counter is then strapped into position over the site of the injection and the rate of

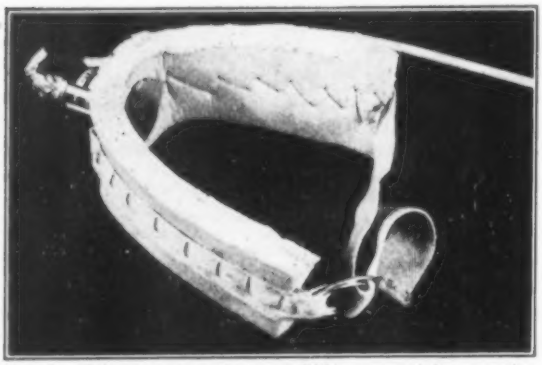

FIG. 2.—Geiger counter tube (type GM4) mounted for strapping on to the calf over $^{24}$Na injection site.

clearance of the $^{24}$Na determined. The ratemeter indicates the gamma-radiation intensity of the injected mass of $^{24}$Na remaining in the muscle at any one time and with the first reading taken to represent 100% activity. The percentage activity is plotted every 30 seconds on a logarithmic scale with time as the abscissa. (Correction is made for the natural decay of the radioactive sodium, which is occurring approximately at the rate of 0.5% every six minutes.) The slope of the resulting graph is an indication of the rate at which the radioactive sodium is being carried away from the injection site.

As an alternative but rather simpler method of recording the rate of clearance of the $^{24}$Na the ratemeter can be connected to a recording milliammeter. The records obtained in this way give exponential curves, but changes in clearance rate can still be easily detected (Figs. 4 and 5).

As the test is most often used in investigating the blood supply of calf muscles the technique for this procedure will be described in detail. As a routine it has been the practice to test the lateral head of the gastrocnemius muscle first. The patient is prepared for the test by getting him to don a pair of running-shorts in place of his pants and trousers. He keeps on his outdoor shoes and his socks. After a half-hour period of rest he is asked to stand up and steady himself with his hands against a suitably placed horizontal bar. The injection is now made into his calf and the counter strapped on. Readings are begun at once, recordings being taken every half-minute. As soon as the clearance rate at rest is seen to be steady over a period of 3–4 minutes the patient is asked to raise the leg not under test clear

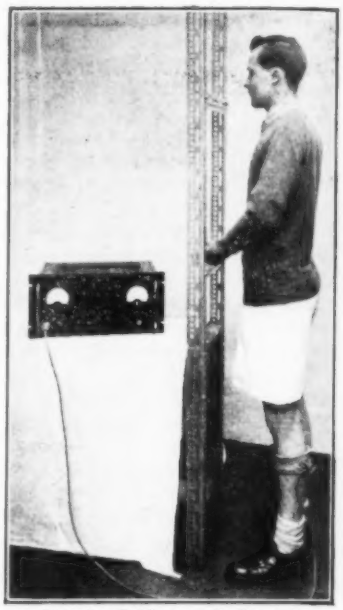

FIG. 3.—Subject ready for test.

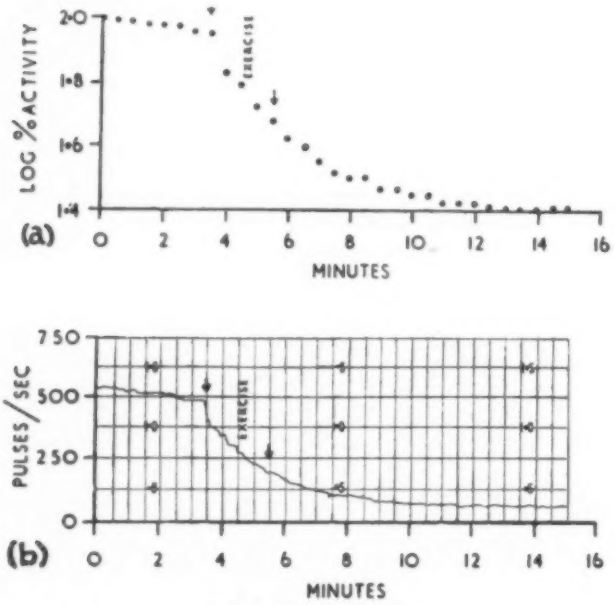


FIG. 4.—Normal subject.

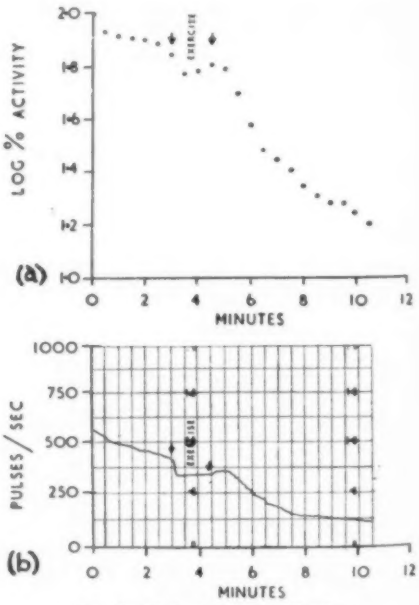


FIG. 5.—Patient with claudication.

Comparison of records of $^{24}$Na clearance from the lateral head of right gastrocnemius muscle as obtained simultaneously by (*a*) plotting against time the log of the percentage activity remaining at the injection site, and (*b*) using a direct recording milliammeter connected to the ratemeter.

of the ground so that he is standing on one leg. He is then asked to exercise by raising himself up on to the toes of the leg under investigation and down again in time with a metronome which beats every second. He thus completes one cycle of up on to the toes and down again every two seconds. He continues to exercise for two minutes unless stopped previously by pain. When he stops he places both feet on the ground and remains standing at rest for a further few minutes until the resting $^{24}Na$ clearance rate is re-established. The test for that particular muscle is then ended. A muscle in the other leg or another muscle in the same leg can then be tested.

As a rough guide it is estimated that the amount of radiation that a patient will receive from the two doses of radioactive sodium used in testing two muscles will be about equal to that received from one chest radiograph. It has been the policy not to give more than two injections of radioactive sodium on any one day and not to retest until eight weeks have elapsed.

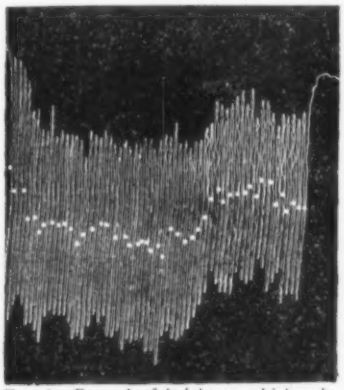

FIG. 6.—Record of height to which subject raises himself every two seconds. (Changes in the mean height are also shown.)

One refinement of the test, which although not essential gives useful information, is to measure the work done by the patient during the test. This can be done very simply by measuring the height in feet to which the patient raises himself on each occasion when he rises on tiptoe and multiplying the total of these heights by his body weight in pounds. The result gives the work done in ft./lb. The height to which the patient raises himself when on his toes is recorded on a kymograph drum by a writing-point connected to a board which rests on the patient's head and moves up and down as he raises or lowers himself (Fig. 6).

### Experimental Evidence on Which the Test is Based

Full details of the experimental basis for this test have been previously published (Walder, 1953; Walder, 1955). Animal experiments were carried out on the isolated skinned limbs of cats and rabbits, and it was found that changes in the rate of clearance of radioactive sodium injected into the muscles as isotonic NaCl were directly related to changes in the rate of blood flow through the muscle as estimated by direct measurement. This relationship held good within the physiological range of blood pressure and flow rates.

In man the relationship between change in muscle blood-flow rates and clearance rates of radioactive sodium was investigated during post-exercise hyperaemia, when flow rates as high as 30 ml./100 g./min. could be obtained and a statistically highly significant linear relationship demonstrated.

### Interpretation of Results

In a subject with a normal circulation the changes in clearance rate during a test are as follows. First, during the initial period of standing, $^{24}Na$ is seen to be cleared from the muscle at a constant but comparatively slow rate. Once the patient starts to exercise, the rate of clearance shows a sharp increase, which persists during the exercise period. When the exercise stops, the clearance rate decreases and within a very short time has returned to its resting clearance rate (Fig. 4).

In a subject with vascular insufficiency of the calf muscles the clearance rate during the initial standing period is not appreciably different from that of a normal patient; but as soon as the exercise starts, instead of an increase in blood flow there is a complete cessation of clearance, and as soon as the subject stops exercising (either because he is told to do so or because he is forced to by the severity of the ischaemic pain of muscle) the clearance of $^{24}Na$ is re-established and there is a period of several minutes when the clearance rate is high (higher, that is, than the initial standing period rate). This high rate gradually subsides, until eventually the resting conditions are re-established (Fig. 5).

### Discussion of Results

In the subjects with a deficient blood supply it is often noted that at the beginning of exercise there is a sudden drop in the counting rate preceding the period when no clearance occurs; then as the patient tires towards the end of the exercise period the counting rate gradually rises, sometimes almost to the pre-exercise level, until finally, after the patient has stopped exercising, the counting rate falls again and the post-exercise phase of rapid clearance is established. Occasionally, if the patient with a deficient blood supply is able to maintain a constant degree of exercise right up to the end of the exercise period, there is a sudden increase in the counting rate almost to the pre-exercise level after the patient has stopped exercising and before the phase of rapid clearance is seen.

At first it was thought that these changes might be explained by the sudden ejection of a large volume of venous blood containing radioactive sodium at the first contraction of the muscle with the reflux of this radioactive blood into the muscle at the end of the exercise phase. However, this explanation cannot be substantiated by experimental evidence; on the contrary, by using special apparatus consisting of multiple counters surrounding the limb under test, it can be shown that the sudden decrease in counting rate sometimes seen at the beginning of the exercise phase, the rise in counting rate towards the end of the exercise, and the sudden rise in counting rate after the patient stops exercising are due to axial movement of the sodium source in relation to the counter as the muscle belly moves with the contractions. The contractions become less as the patient tires towards the end of exercise (Fig. 6), and finally the muscle returns to its resting position when the exercise stops.

The physical characteristics of the recording milliammeter used in this work are such that its frequency response is rather low, and consequently only the mean of these axial movements is recorded. When a more sensitive recording instrument such as an oscilloscope is used with a higher frequency response these axial movements can be demonstrated (Fig. 7).

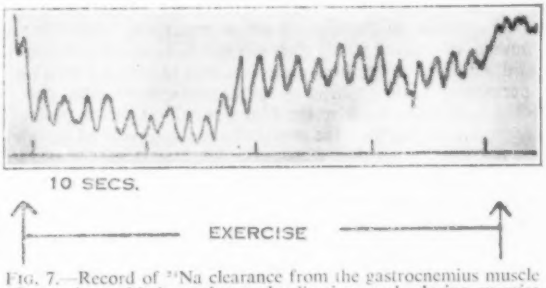


FIG. 7.—Record of $^{24}Na$ clearance from the gastrocnemius muscle of a patient with intermittent claudication made during exercise using an oscilloscope with camera as the recording instrument.

An interesting fact which emerges from these experiments is that in a patient with peripheral vascular disease affecting the muscles there is often a complete cessation of blood flow during the type of exercise used in this test. Since there is a very rapid clearance rate as soon as the exercise is stopped, it would appear that the muscle vessels are opening up normally during exercise; but presumably the internal resistance of the muscle during contraction is too great for

the available head of pressure in the arterial blood at the entrance to the muscle to force the blood through during exercise.

Some experiments on the lines of those reported by Barcroft and Dornhorst (1949) have been carried out on normal subjects and on patients with peripheral vascular disease in an effort to demonstrate how the tension developed in the gastrocnemius muscle affects the blood flow through it.

Measurements of radioactive sodium clearance are made on the calf muscle of a subject who is lying on a couch. Changes in tension within the calf muscle can be brought about by arranging for the subject to depress a weighted pedal with his foot. The weights on the pedal can be varied. In a patient with claudication the circulation stops completely at tensions which in the normal subject result only in a slowing of the blood flow (Fig. 8).

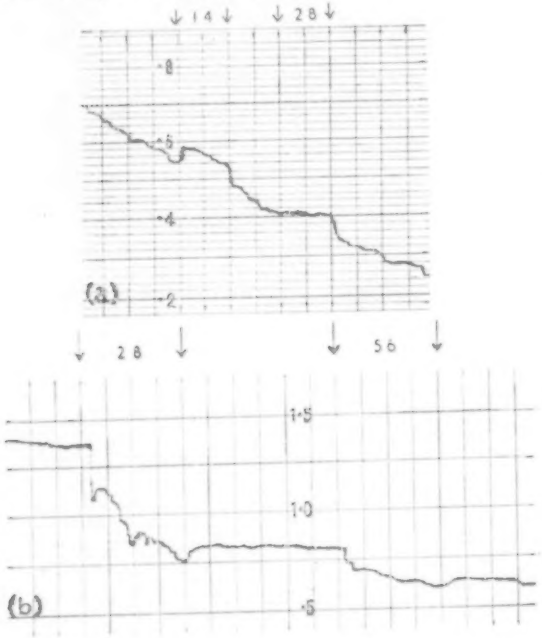


FIG. 8.—Effect on the clearance rate of $^{24}Na$ from the gastrocnemius muscle of increasingly powerful contractions. The figures 14, 28, and 56 refer to the load in pounds supported by the contracting calf muscle. (*a*) Patient with claudication; clearance has stopped with a load of 28 lb. (*b*) Normal subject; clearance still continues with a load of 56 lb.

The results of the clinical experiments carried out in the course of investigating the clearance rate of radioactive sodium serve to emphasize the fact that in patients who have peripheral vascular disease severe enough to give rise to claudication on exercise the blood supply at rest is perfectly adequate to maintain the metabolic requirements of muscle.

These facts become important when considering the use of drugs for the treatment of intermittent claudication. So far no drug tested in this clinic has been found to change the abnormal clearance curve of a patient with peripheral vascular disease to the "normal" type of clearance curve. There is no doubt that some drugs result in vasodilatation of blood vessels in resting muscle even to the extent of doubling the resting blood flow; this does not, however, enhance the flow in exercise, since even when the maximum vasodilatation resulting from metabolites has occurred the flow during contraction is still zero. It is not an increased vasodilatation of muscle blood-vessels that is required but an increased head of pressure at the entry port of the vessels into the muscle so that blood can flow even when the internal tension of the muscle is high owing to contraction.

The operation of lumbar sympathectomy (that is, the removal of a length of lumbar sympathetic chain from above the first lumbar ganglion to below the third lumbar ganglion) has not been found to affect an abnormal $^{24}Na$ clearance curve.

A few cases have been followed in which vascular grafting has been carried out for a localized block in a major peripheral vessel. After some successful grafting operations it has been possible to demonstrate the return of an abnormal sodium clearance curve to an apparently normal type of curve, with clinical relief of the claudication (Fig. 9). In these cases it is sometimes possible to re-establish the peripheral blood flow so fully that the pressure head of blood available in the arteries to the gastrocnemius muscles is once again capable of maintaining an adequate flow against the resistance of the contracting muscle.

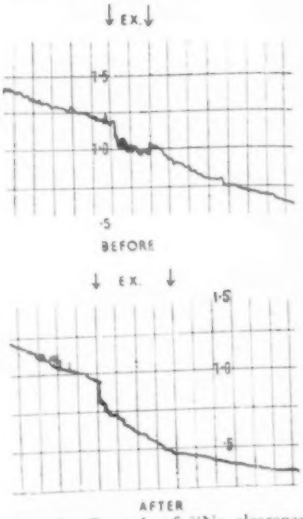


FIG. 9.—Records of $^{24}Na$ clearance from the right human gastrocnemius muscle made before and after the replacement of a blocked aortic bifurcation by a homograft. (↓ Ex. ↓ indicates period of exercise.)

It is possible for normal $^{24}Na$ clearance curves for all the calf muscles to be obtained in the presence of claudication, but such cases will have a grossly lowered haemoglobin concentration. Correction of the anaemia will cure the claudication.

## Summary

An objective test is described using radioactive isotopes for the evaluation of vascular sufficiency in muscle during exercise. The apparatus is readily available commercially, and in fact is already possessed by most hospital physics departments. This test assists in the diagnosis of intermittent claudication by giving additional evidence in doubtful cases. It enables vascular insufficiency to be detected early. The exact muscle affected can be located. The test also enables treatment to be assessed objectively.

The technique described provides a useful tool for research into the problems of muscle blood flow. Observations made so far using this technique would seem to suggest that the fundamental requirements in claudicating muscles are an increase in the pressure of blood available in the arteries supplying the muscle or a decrease in the tension developed within the muscle during contraction.

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The Ministry of Health has sent to local authorities a new edition of its memorandum entitled *Food Poisoning* (revised 1958, H.M.S.O., 1s.). It brings up to date the 1949 edition but makes no major changes. The memorandum is intended primarily to help medical officers of health. A covering letter stresses the importance to the Ministry of having adequate information about outbreaks of food-poisoning. It also asks local authorities whether there is need to remind medical practitioners "of the value of full and prompt notification of cases of food-poisoning and of their obligations in regard to such notification."

# INFLUENZA A (ASIAN) 1957

## CLINICAL AND EPIDEMIOLOGICAL FEATURES IN A GENERAL PRACTICE

BY

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It is only in the community at large that the true natural patterns of many of the common diseases can be accurately and rationally appreciated, and the general practitioner is probably the medical man best equipped to study such conditions in his own local community. This applies with particular force to the study of the effects of an influenza epidemic. With such a highly infectious yet relatively mild condition the majority of those affected will either treat themselves or remain entirely under the care of their family doctor. Very few will require admission to hospital on account of complications and fewer still will die and be recorded by the Registrar-General.

It is the general practitioner who is able to provide the most accurate picture of an epidemic such as the one just past, but even he will underestimate the total prevalence, as many of his patients will not consult him on account of the mildness of the infections. His figures will put those from hospitals, quoting serious complications and deaths, in their correct perspective.

This paper reports the effects of the recent influenza A epidemic on a south London suburban practice during the period September to November, 1957. The numbers at risk in the practice are shown in Table I.

TABLE I.—*Numbers at Risk in Practice*

| Age: | 0– | 1– | 5– | 10– | 20– | 30– | 40– | 50– | 60– | 70– | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No. | 70 | 384 | 455 | 600 | 712 | 875 | 852 | 753 | 488 | 332 | 5,521 |

*Diagnostic Criteria.*—" 'Flu " tends to be rather a lax and facile label given to many short-term infections of the respiratory tract of indefinite aetiology. It is almost certainly an inaccuracy when applied during inter-epidemic periods but probably highly accurate when an epidemic is raging, especially when typical cases randomly selected are proved serologically to show evidence of recent infection with influenza A (this was so in this epidemic). Here the diagnosis of influenza was restricted to patients with a sudden onset, considerable systemic disturbance, and symptoms referable to the respiratory tract. Even so, it is probable that there was some inflation of numbers by including some patients suffering from the common prevailing seasonal respiratory infections; but this was more than compensated for by the numbers who did not seek medical attention for one reason or another.

### Incidence

The first cases of influenza were seen in the first week in September, and the peak was reached in mid-October (Table II). The *age distribution* of these cases that were actually seen, diagnosed, and treated is shown in Table III. There were no appreciable sex differences. The age of maximal liability was between 5 and 20, and there was a striking freedom from infection in the elderly.

Whilst there are records of 930 patients who were seen, diagnosed, and treated, a very large number of patients in the practice who were infected did not find it necessary to seek medical attention because they were accustomed to coping themselves, because they were secondary cases in the household and knew the routine care, or because they did not require any certification for absence from work. It is difficult to estimate these numbers with any accuracy, but possibly some further 300–400 patients were infected in this practice, giving an approximate total incidence rate of 25%. If this rate was representative of the country as a whole, and it is believed that it was, then between 10 and 15 million persons in the British Isles suffered infection—a truly astounding figure. The rate of infection in this particular epidemic was much higher than in three previous epidemics recorded in 1951, 1953, and 1955, when the corresponding rates for estimated total incidence were between 5 and 10%.

TABLE II.—*New Cases of Influenza September–November, 1957*

| | September | | | | | October | | | | Nov. | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Week: | 2 | 9 | 16 | 23 | 30 | 7 | 14 | 21 | 28 | 4 | |
| No. of new cases | 15 | 34 | 61 | 102 | 148 | 160 | 204 | 146 | 52 | 8 | 930 |

TABLE III.—*Age Distribution of Influenzal Cases*

| Age: | 0– | 1– | 5– | 10– | 20– | 30– | 40– | 50– | 60– | 70– | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No. of cases | 12 | 92 | 138 | 218 | 127 | 111 | 103 | 72 | 43 | 14 | 930 |
| % of those at risk | 18 | 24 | 30 | 36 | 18 | 13 | 12 | 10 | 9 | 4 | 17 |

It was commonplace to see whole families go down together, either simultaneously or one after the other. The *incubation period* appeared to be between 48 and 72 hours.

The first wave of infection affected principally those aged 11 to 18. Next followed a spread to younger children and older members of their households. By the third and fourth weeks the epidemic was less discriminating regarding age distribution.

### Clinical Features

The *onset* was striking in its suddenness—the time could often be given to the minute. The *initial symptoms* were malaise and variable degrees of prostration, chills, aching back, head, and limbs, a running nose, rawness in the throat and chest. A dry and explosive cough soon developed and sputum when present was inconspicuous and mucoid in character. Profuse sweats were accompanied by a fever up to 106° F. (41° C.).

Examination revealed a sick, prostrated, and feverish patient. The pulse rates corresponded to the height of the fever, but in some cases an excessive bradycardia was noted. Abnormal signs in the respiratory tract were relatively insignificant. The fauces were reddened, but not excessively so. Erythematous patches were often noted on the palate. The ears were normal in all except the 9 cases in which an acute otitis media developed. No abnormalities were detected in the chest, apart from the 28 patients who developed complications. The eyes were not abnormally reddened when the high fever and general flushing and hyperaemia were taken into account. Gastro-intestinal disturbances such as vomiting and diarrhoea were most unusual. Epistaxis occurred in 10 children. Enlargement of the post-occipital glands was not infrequent in young children and a faint macular–erythematous rash was noted in four instances.

### Course and Management

The acute phase lasted an average of three to five days and was followed by a slow and often prolonged convalescence. The period "off work," in those at work, averaged 10 to 14 days. The degree of post-influenzal depression and debility appeared less profound than in previous epidemics. In 18 patients of all ages an apparent *recurrence* of symptoms took place some 10 to 21 days from the initial onset. This recurrence, although prolonging the duration of the illness, was not associated with any increased liability to complications.

The management was essentially symptomatic, with analgesics and linctuses as the basic remedies. No attempts at chemoprophylaxis were employed in any patient, and antibiotics were found necessary in only 24 patients with complications. Penicillin by intramuscular injection was used in 20 and oxytetracycline in 4.

## Complications

The medical importance of influenza lies in the extent and severity of its complications. It is gratifying to report that the incidence of complications in this epidemic was extremely low and that when they did occur they were of a relatively mild nature. No patient required admission to hospital and no patient died from direct or indirect effects of influenza.

The complications that did occur were seen only in the ears and the chest. During the period of the epidemic 28 patients were seen with acute chest infections and 9 with acute otitis media complicating influenza. This represents a complication rate of 3% for acute chest infections and 1% for acute otitis media, a total of 4%.

In order that the effects of the influenza epidemic on the incidence of acute chest infections and acute otitis media may be appreciated, comparison can be made with the incidence of these two types of infection, and also of acute tonsillitis, during the same period (September to November) over the past four years (Table IV). Only small numbers

TABLE IV.—*Incidence of Acute Respiratory Infections, 1954–7*

| | Acute Chest Infections | Acute Otitis Media | Acute Tonsillitis |
|---|---|---|---|
| 1957 .. | 28 | 15 (9 following 'flu) | 7 |
| 1956 .. | 10 | 18 | 12 |
| 1955 .. | 5 | 17 | 20 |
| 1954 .. | 8 | 16 | 15 |

are involved, but it is of interest to note that, while there was a very significant rise in the number of acute chest infections in 1957, there was no corresponding rise in acute middle-ear infections and a distinct fall in acute tonsillitis. The explanation of these trends is elusive, but it does confirm the findings of Dr. G. Keith Hodgkin, who reported at the Annual Meeting of the British Medical Association at Newcastle upon Tyne (1957) that the incidence of acute streptococcal infections is often much lower before and during an influenza epidemic.

*Chest Complications.*—The ascertainment of a chest infection in general practice is essentially a clinical matter and depends on the presence or absence of abnormal physical signs in the chest in a patient with other evidence of general and local infection. Acute chest infections were diagnosed when abnormal physical signs were present in the chest. They were grouped into those suffering from *acute bronchitis*, with diffuse and bilateral rales and rhonchi, and *pneumonia*, when moist sounds were local and unilateral (in no instance was clinical consolidation a feature). The incidence of these two groups is shown in Table V.

TABLE V.—*Incidence of Acute Chest Complications*

| Age: | 0– | 1– | 5– | 15– | 20– | 30– | 40– | 50– | 60– | 70– | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pneumonia .. | — | — | 3 | 3 | 1 | 3 | 1 | 3 | 2 | 2 | 18 |
| Acute bronchitis .. | — | 2 | 1 | 1 | 2 | — | 1 | 1 | 2 | — | 10 |
| Total .. | — | 2 | 4 | 4 | 3 | 3 | 2 | 4 | 4 | 2 | 28 |
| % in those with 'flu (See Table III) | — | 2 | 3 | 2 | 3 | 3 | 2 | 5 | 9 | 15 | 3 |

The risk of chest complications rose appreciably after the age of 50, but even so the proportions were small. These complicating infections were of a mild to moderate severity, no patient requiring admission to hospital and no one dying. Antibiotics were used in 20 of these 28 episodes. Chest complications prolonged the duration of the illness up to 14–28 days.

Investigations showed that segmental areas of consolidation were present in 18 who were radiographed, and bacteriological examination of the sputum in 11 instances showed the predominating organism to be pneumococcus in three, *Streptococcus viridans* in seven, and *Haemophilus influenzae* in one.

Of these 28 patients with chest complications, only 7 were known "chronic bronchitics." In the practice there are 150 known chronic bronchitics, therefore only 4.5% developed any acute exacerbations during this epidemic. The explanations for this low rate are probably the timing of the epidemic, before the seasonal bad weather, and the fact that it was the lower age groups who were most liable to influenza rather than those in the "bronchitic" period of life—that is, over 50.

*Ear Complications.*—During the period of the epidemic 15 new cases of acute otitis media occurred in the practice, but in only nine of these was influenza a contributory factor. The age incidence of these nine is shown in Table VI. The

TABLE VI.—*Incidence of Acute Otitis Media*

| Age: | 0– | 1– | 5– | 10– | 20– | 30+ | Total |
|---|---|---|---|---|---|---|---|
| No. .. | 1 | 2 | 2 | 2 | 1 | 1 | 9 |

course in these few cases was uneventful. The cases were mild and in only four were antibiotics necessary to control the infection.

## Effects of the Epidemic on Normal Pattern of Respiratory Infections

This epidemic has been the greatest incident of infectious disease that has ever occurred in this practice. The only previous episode that compares with it were the effects of the severe fog in December, 1952, but then the effects were short-lived and sharp reactions to an irritant of limited duration, rather than a spreading infection over two months that affected a quarter of the practice population.

To appreciate the effect of the epidemic more dramatically it is useful to compare the weekly volume of work in the practice for the common respiratory infections in the corresponding weeks over the past six years (Table VII). At

TABLE VII.—*Weekly Attendance Rates for Respiratory Infections September and October, 1952–7*

| Week | 1952 | 1953 | 1954 | 1955 | 1956 | 1957 |
|---|---|---|---|---|---|---|
| 1st week in September .. | 45 | 32 | 36 | 35 | 70 | 72 |
| 2nd .. .. .. .. | 75 | 54 | 58 | 36 | 84 | 108 |
| 3rd .. .. .. .. | 82 | 65 | 60 | 45 | 80 | 194 |
| 4th .. .. .. .. | 65 | 95 | 69 | 83 | 112 | 205 |
| 1st .. .. October .. | 71 | 99 | 76 | 88 | 150 | 346 |
| 2nd .. .. .. .. | 63 | 85 | 58 | 64 | 112 | 316 |
| 3rd .. .. .. .. | 68 | 104 | 63 | 76 | 120 | 265 |
| 4th .. .. .. .. | 79 | 112 | 78 | 111 | 111 | 201 |

the peak in 1957 there were five times as many attendances for respiratory infections (either visits or consultations) than in 1952 and more than five times as much work because many more visits were required, and visiting is much more time-consuming than consulting at the surgery.

## Comparison with Previous Influenza Epidemics

Over the past 10 years three previous influenza epidemics have been observed and recorded in this practice—influenza A in 1950–1 and 1953 and influenza B in 1955. Comparison of the *total incidence and that at various ages* and also the totals of the patients seen, diagnosed, and treated shows certain similarities and differences (Table VIII).

TABLE VIII.—*Age Incidence in Percentages of Those at Risk of Influenza Epidemics of 1950–1, 1953, 1955, and 1957 in a General Practice*

| Ages: | 0– | 1– | 5– | 10– | 20– | 30– | 40– | 50– | 60– | 70+ | Total No. | Whole Practice |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1950–1 (A) .. | — | 1 | 2 | 4 | 6 | 8 | 4 | 10 | 5 | 4 | 6 | 223 |
| 1953 (A) .. | — | 1 | 2 | 4 | 10 | 5 | 8 | 8 | 8 | 2 | 6 | 264 |
| 1955 (B) .. | 2 | 5 | 7 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 3 | 150 |
| 1957 (A) .. | 18 | 24 | 30 | 36 | 18 | 13 | 12 | 10 | 9 | 4 | 17 | 930 |

The influenza A epidemics of 1950–1 and 1953 were similar in extent and in age distribution, while the epidemic of influenza B in 1955 was less extensive and a little more likely to affect young children. The present epidemic of influenza A was very much more extensive, nearly three times as great as the two previous A epidemics, and affected young persons and children to a dramatic degree.

Comparison of the *incidence of the various chest complications* also reveals striking differences (Table IX). The highest rates of complications were noted in the 1950–1 epidemic, when 20% of those seen developed chest complications. The A epidemic of 1953 and the B epidemic of 1955 both had around 10% of complications, whereas the present epidemic had a rate of only 3%—a remarkable difference.

TABLE IX.—*Chest Complications of Influenza Epidemics of 1950–1, 1953, 1955, and 1957*

| | 1950–1 (A) | 1953 (A) | 1955 (B) | 1957 (A) |
|---|---|---|---|---|
| No. of 'flu cases .. | 223 | 264 | 150 | 930 |
| Chest complications .. | 43 (20%) | 29 (12%) | 15 (10%) | 28 (3%) |
| Pneumonias .. | 37 (17%) | 17 (7%) | 11 (7%) | 18 (2%) |
| Acute bronchitis .. | 6 (3%) | 12 (5%) | 4 (3%) | 10 (1%) |

All these comparisons suggest that there are real differences between each influenza epidemic, the extent varies, and each has its own predilections for certain age groups, and each has different rates of complications. These differences probably depend on such factors as the virulence and the antigenic strains of the virus, past experience of the community with that particular strain of virus, the time of the year that the epidemic strikes, and the prevailing climatic conditions at that time. Would the rate of complication have been higher if the present epidemic had struck in midwinter with severe cold, damp, and fog?

As regards the immediate future, it is difficult to forecast the further course of this epidemic, but from the past experience of previous epidemics there is little reason to believe that a "second wave" will strike in the coming winter months. Apart from the epidemic of 1918–20 this has not been a feature of influenza.

The use of *vaccines* would appear to have a very limited place in the management and prevention of influenza. For these to be effective they would need to be administered a reasonable time before the epidemic arrived; a good deal of warning would have to be available in order to prepare the vaccine in time, and in view of the unique nature of each epidemic a new vaccine would have to be prepared for each successive epidemic; and, finally, in view of the almost certain insufficiency of supplies, the choice of the recipients for the vaccine would be a delicate and unwelcome task.

### Conclusions

This report of the clinical and epidemiological effects of the recent influenza A epidemic on a single south London practice confirms the characteristics that have already been reported. The experiences in this particular practice show that it was a very widespread infection affecting predominantly young persons, but that it was of a relatively low degree of virulence. However, in an epidemic that has probably affected between 10 and 15 million persons in the British Isles the fortunate experience of this practice, in having no deaths, was not universal, and it is also probable that at least 5,000 persons died from direct or indirect effects of the epidemic, a rate of 1 death for every 2,000–3,000 cases of influenza.

### Summary

A report is presented on 930 cases of influenza A (Asian) seen during the recent epidemic in a south London general practice.

These cases represent an incidence of 17% in the practice, but it is estimated that at least 25% of the population at risk were affected. Highest rates were recorded in children aged 5–10 (30%) and in teenagers (36%).

The clinical features were those common to all influenza epidemics—a sudden onset, marked prostration and fever, respiratory tract symptoms, and a slow and prolonged convalescence.

There was a low rate of complications—only 4%. Acute chest infections accounted for 3% and middle-ear infections for 1%. All these infections were mild and cleared satisfactorily at home with antibiotics. No patient required admission to hospital and no patient died from the effects of influenza.

The epidemic produced a fivefold rise in the volume of work in the practice.

Comparisons with previous epidemics of 1950–1 (influenza A), 1953 (A), and 1955 (B) show marked differences in age distribution and rates of complications.

It is probable that each influenza epidemic has a pattern and character of its own, with a varying extent of spread, age distribution, virulence, and complication rate. With the present epidemic it is considered unlikely that "second waves" will occur. Vaccines have a very limited practical place in prevention.

The present epidemic has been mild but extremely widespread. It is estimated that some 10–15 million persons were infected in this epidemic and that around 5,000 persons have died from direct or indirect effects of influenza, giving a rate of 1 death for 2,000 to 3,000 cases of influenza.

The assistance given by Mrs. K. Sabel, Miss E. B. Blake, and Dr. E. M. Hume is gratefully acknowledged.

REFERENCE

*Brit. med. J.*, 1957, 2, 226.

# A TRIAL OF PENICILLIN AND CHLORTETRACYCLINE IN TREATMENT OF BRONCHITIS*

## REPORT FROM THE CITY GENERAL HOSPITAL, SHEFFIELD

The successful antibiotic treatment of acute exacerbations of chronic bronchitis remains uncertain, despite the wide choice of theoretically suitable agents now available. The high incidence of bronchitis in this form and the high mortality rate resulting from the disease make it essential to select the most reliable of these remedies without recourse to extensive preliminary investigations. Moreover, the chosen drug should be effective when given orally and its toxicity should be low enough to permit safe domiciliary use. The principal aim of this trial was to decide which of the two antibiotics, penicillin by injection and chlortetracycline ("aureomycin") orally, was the more effective in the treatment of bronchitis. This paper records the clinical and bacteriological results obtained.

### Selection of Patients

All patients were adults suffering from an acute exacerbation of bronchitis, and all had emphysema of varying degree. They were admitted as emergencies to medical wards. Those who had received a sulphonamide or an antibiotic within the previous two weeks were excluded, as were cases of asthma or tuberculosis. The patients were divided into two groups—those who appeared to be suffering from bronchitis only, and those in whom bronchitis was complicated by congestive heart failure of pulmonary origin. Subsequent investigation proved the diagnosis of bronchitis wrong in 11 cases, which were then rejected from the series. Similarly, in 10 cases heart failure was found to be due to other causes and these also were eliminated from the trial. Finally there were 47 cases of uncomplicated bronchitis and 37 cases of bronchitis with pulmonary heart failure.

*Those taking part in the study were:—*Clinicians:* Drs. F. J. Flint, R. W. Meikle, J. E. Middleton, and T. L. Morris. *Bacteriologists:* Drs. E. H. Gillespie, M. Pownall, and J. E. M. Whitehead.

### Treatment

The cases were allocated to one or other of the two treatment groups at random by a similar method to that used in the Medical Research Council (1951) trial of antibiotics in the treatment of pneumonia. To one group sodium penicillin G was given intramuscularly in doses of at least 200,000 units six-hourly for 72 hours; this was followed every 12 hours by a single intramuscular injection of 600,000 units of procaine penicillin with 200,000 units of potassium penicillin G. The cases treated with chlortetracycline received 0.25 g. by mouth four-hourly for 72 hours, and 0.25 g. six-hourly thereafter. A minimum of 10 days' therapy was recommended, and the physician in charge was permitted to change the treatment if there was no clinical improvement.

### Investigations

These included a four-hourly temperature chart, a leucocyte count, an *x*-ray examination of the chest which was repeated once, and an electrocardiogram. Before treatment began a specimen of sputum was obtained, and thereafter 24-hour collections of sputum were made in specially labelled cartons. The first sample of sputum was examined directly, cultured, and inoculated into mice; these procedures were repeated, with the exception of mouse inoculation, each week. Any pneumococci present were typed and the sensitivity to penicillin and chlortetracycline of the various pathogenic organisms found was assessed weekly. The daily sputa were all weighed and then examined by naked eye for pus and blood. Paired sera were taken from each case for estimation of the titre of antibodies to influenza A and B viruses and the psittacosis group.

*Comparability of Treatment Groups.*—The treatment groups were found to be comparable with respect to age, sex, the number of days' illness before admission, and the numbers who were desperately ill at the time of admission (Table I).

TABLE I.—*Comparability of Groups at Start of Treatment*

| Group | Antibiotic | No. of Cases | Average Age | Sex | | No. of Days' Illness Before Admission (Medians) | No. Desperately Ill on Admission |
|---|---|---|---|---|---|---|---|
| | | | | M | F | | |
| Bronchitis with cor pulmonale | Penicillin | 19 | 63 | 16 | 3 | 11 | 1 |
| | Chlortetracycline | 18 | 55 | 16 | 2 | 9 | 1 |
| Bronchitis only | Penicillin | 23 | 59 | 15 | 8 | 7 | — |
| | Chlortetracycline | 24 | 61 | 12 | 12 | 10 | — |

### Clinical Results of Treatment (Table II)

In the trial 84 patients were included, and equal numbers were treated with penicillin and chlortetracycline. Of these 84 patients 10 died (11.9%), five in each treatment group; 47 cases suffered from bronchitis only and two (4.3%) died; 37 patients also had heart failure, and out of this group eight (21.6%) died.

Treatment with penicillin was changed in 16 cases, 13 of which subsequently recovered, whereas only two in the chlortetracycline group required a change of antibiotic. Of the 10 fatal cases, four required a change of treatment—three on penicillin and one on chlortetracycline. Thus the "total failures"—that is, those who died plus those in which treatment was changed—numbered 16 on penicillin but only six on chlortetracycline. Patients who neither died nor required a change of treatment were designated "survivors"; these numbered 24 (57%) in the penicillin group and 36 (86%) treated with chlortetracycline.

TABLE II.—*Clinical Results of Treatment*

| Groups | Penicillin | | Chlortetracycline | |
|---|---|---|---|---|
| | Bronchitis with Cor Pulmonale | Bronchitis Only | Bronchitis with Cor Pulmonale | Bronchitis Only |
| Deaths | 4 | 1 | 4 | 1 |
| Treatment changed (No. of cases) | 7 | 7 | — | 2 |
| Total failures (Nos. with change of treatment and deaths before change of treatment) | 9 | 7 | 4 | 2 |
| Survivors | 8 | 16 | 14 | 22 |
| Total cases (bronchitis with cor pulmonale 37; bronchitis only 47) | 19 | 23 | 18 | 24 |

TABLE III.—*Duration of Fever and Stay in Hospital (Survivors)*

| | 24 Cases on Penicillin | 36 Cases on Chlortetracycline |
|---|---|---|
| Days of fever (medians) | 6 | 2·5 |
| No. of cases in hospital < 3 weeks | 15 | 25 |
| " " " " " > 3 " | 9 | 11 |

Naked-eye changes in the purulence of sputum bore no obvious relation to the antibiotic used. The daily weight of sputum, however, fell appreciably in more than half of the surviving cases, but the difference in effect of chlortetracycline and penicillin in this respect was not significant.

Table III illustrates the duration of fever and of hospital-stay in the survivors. Again the figures favour chlortetracycline with regard to the disappearance of fever. On the other hand, the proportion of cases detained in hospital for more or for less than three weeks was the same in both treatment groups.

Radiography of the chest provided no information which could be related to the clinical recovery of the patient.

### Bacteriological Results of Treatment

Pneumococci and *Haemophilus influenzae* were the predominant pathogenic organisms in the sputum. Cultural examination of the sputum on admission yielded pneumococci from 51 patients (61%) and *H. influenzae* from 35 (42%). Typing of the strains of pneumococci isolated showed no significant difference in distribution of types between the two treatment groups.

TABLE IV.—*Bacteriological Results of Treatment*

| Antibiotic | Total No. of Cases | Organisms | Primary Culture (No. of Cases) | Secondary or Later Culture (No. of Cases) | Secondary Infection with Resistant Organisms (No. of Cases) |
|---|---|---|---|---|---|
| Penicillin | 42 | Pneumococci | 27 | 1 | 28 (67%) |
| | | *H. influenzae* | 19 | 20, incl. 9 which retained *H. influenzae* | |
| Chlortetracycline | 42 | Pneumococci | 24 | 9 | 12 (29%) |
| | | *H. influenzae* | 16 | One retained *H. influenzae*; three acquired *H. influenzae* after admission | |

Table IV records the effects of treatment as judged by changes in the cultural findings in sputa examined at intervals after the start of treatment. Penicillin and chlortetracycline were equally effective against pneumococci. Against *H. influenzae*, however, treatment with penicillin failed to eliminate this organism from the sputum of 9 patients, and in a further 11 cases it was isolated for the first time during penicillin therapy. Only one patient who received chlortetracycline retained *H. influenzae*, but this organism was isolated from three during treatment. Pneumococci were found in the sputa of the five fatal cases treated with penicillin; two of these were also infected with penicillin-sensitive Friedländer's bacilli and two others developed resistant coliform organisms. One patient died before a specimen of sputum could be collected. No chlortetracycline-resistant organisms were found in the five fatal cases treated with this antibiotic; pneumococci were found in four cases, *H. influenzae* in three cases, and Friedländer's bacilli in one case. None of the pneumococci isolated from any of the fatal cases belonged to Types I, II, or III.

The bacteriological findings in the 16 cases which required a change of treatment were not significantly different from those in other cases, with the exception of three penicillin-treated cases in which resistant forms of *H. influenzae* were found. Secondary infection with antibiotic-resistant organisms, however, was much commoner in all cases given penicillin (28 out of 42) than in those treated initially with chlortetracycline (12 out of 41).

Virus studies showed that there was serological evidence of recent infection by influenza virus A in 10 patients, by influenza virus B in one patient, and by a virus of the psittacosis group in another patient. Of these 12 patients, nine were given chlortetracycline and three penicillin.

### Comment

Pneumococci and *H. influenzae* appear to be the most important pathogenic organisms consistently found in the sputa of patients suffering from bronchitis (May, 1953). The frequency with which they may be isolated from the sputum of such patients has been confirmed in the present trial; moreover, out of 10 fatal cases the sputum of nine contained pneumococci and that of four had *H. influenzae*. Clearly, therefore, treatment should be designed to eliminate these two organisms, preferably by using a single antibiotic. It has been suggested (*Brit. med. J.*, 1954; Flint, 1954; *Lancet*, 1954) that the tetracyclines are more effective for this purpose than penicillin. In this series of cases the results throughout favoured treatment with chlortetracycline, and patients who received penicillin more often required a change of antibiotic on clinical grounds alone. It is probably of greater significance, however, that the penicillin-treated cases were more readily infected with *H. influenzae* during treatment than those which received chlortetracycline. Eight of the 10 fatalities occurred in patients who were suffering from heart failure, and there was no apparent difference in the effect of the two antibiotics on these cases.

In the cases which recovered chlortetracycline was apparently more effective than penicillin, whether heart failure was present or not; this result was obtained in spite of the greater incidence of *H. influenzae* in the cases without heart failure. Moreover, there was a higher incidence of recent respiratory virus infection among the cases treated with chlortetracycline. In both diagnostic groups of the series the incidence of pneumococcal infection was equal, thus suggesting that the better effect of chlortetracycline on *H. influenzae* was the deciding factor in favour of this antibiotic. This view is supported by the work of Gabrielsen, Lynn, and Leedham (1954), who showed that chloramphenicol or chlortetracycline was more effective than penicillin in eradicating infection with *H. influenzae*.

Toxic effects were negligible even in those treated with chlortetracycline, thus confirming earlier work from this hospital (*Brit. med. J.*, 1956).

It can therefore be concluded that for routine use chlortetracycline is preferable to penicillin in the treatment of acute exacerbations of bronchitis, regardless of whether the infecting organism is *H. influenzae* or the pneumococcus. All the tetracyclines have similar properties, however, and any one of them could be expected to produce results comparable to those of chlortetracycline.

In this trial no attempt was made to assess the value of penicillin and streptomycin given concurrently; this combination of antibiotics is possibly the most effective treatment for infections with *H. influenzae* (Mulder, Goslings, van der Plas, and Lopes Cardozo, 1952), although large doses by intramuscular injection are essential.

### Summary

A controlled trial of chlortetracycline (" aureomycin ") and penicillin in 84 cases of bronchitis is reported. There were equal numbers of cases in each treatment group, but 37 patients also suffered from pulmonary heart disease.

Pneumococci and *H. influenzae* were the pathogenic organisms most often isolated from the sputum.

Five deaths occurred with each antibiotic; otherwise the results showed that chlortetracycline was the more effective agent and that it appeared to prevent secondary infection with *H. influenzae* and other organisms more readily than penicillin.

Chlortetracycline rarely produces toxic effects at a dosage of 250 mg. six-hourly.

We thank Dr. C. S. Darke, Dr. K. J. G. Milne, Dr. E. G. Rhind, and Professor C. H. Stuart-Harris for permission to study patients admitted to their care. We are grateful to Dr. E. K. Abbott, Dr. S. Varadi, and Dr. A. J. N. Warrack, who carried out radiological, haematological, and post-mortem examinations respectively. Our thanks are also due to Dr. J. R. Wilson, of Lederle Laboratories, who kindly supplied the chlortetracycline (aureomycin) used in this trial.

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## THIRTEEN CASES OF INFLUENZAL BRONCHOPNEUMONIA IN CHILDREN

BY

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During the recent influenza epidemic 13 children whose ages varied between 7 months and 14 years were admitted to hospitals under our care suffering from influenzal bronchopneumonia. Twelve were admitted to the Pontefract General Infirmary and one to the Wakefield General Hospital. Although the epidemic appeared to affect these adjoining towns to the same degree, the incidence of severe cases was much greater in Pontefract and the surrounding area than in the Wakefield district. Four of these children died within 12 hours of being admitted and another died 36 hours after coming into hospital. Of the 13 children, seven were under 3 years of age, of whom one died. There were four deaths in children between the ages of 9 and 14 years.

Only 5 of the 13 children were completely fit before they were overtaken by the influenza, and two of their number died. Of the other eight children one had bronchiectasis together with diabetes; one had a right hemiplegia following birth trauma; one had had measles encephalitis five years previously which had left her with residual bilateral pyramidal tract signs (these three children died); one had residual weakness of both legs following an attack of poliomyelitis one year previously; another had bronchiectasis and a mild anaemia; and the remaining three children had severe anaemias.

### Symptoms and Signs

The illness was characterized by its sudden onset, its rapid progression, and the paucity of physical signs in the chest. The longest history was seven days and the shortest a matter of 12 hours. Where the history was longer than four days

the child was first seen following a relapse. In all 13 cases the symptoms were very similar. The child started with a febrile illness, vomited, became listless and dyspnoeic, and, in the untreated case, progressed to delirium, convulsions, coma, and death within 48 hours. In six cases the child complained of a sore throat, five had a cough, and two complained of chest pain. Only 2 of the 13 children were slightly cyanosed. Headache was a presenting symptom in only one case admitted to hospital, although one of us (J. D. P.) found headache and muscular pains common presenting symptoms in children seen on domiciliary visits.

All but one of the children had elevated temperatures and increased heart and respiratory rates. The case of the one exception is briefly reported.

A boy of 11 had a history of mild fever which settled down after four days, but 36 hours before admission he started vomiting and for 12 hours before admission he was mentally disturbed. On physical examination, however, absolutely nothing was to be found apart from the fact that he resented being examined and voiced his disapproval with high-pitched shrieks. Twelve hours later, however, he developed a spastic paralysis of all four limbs and for the first time signs were heard in the chest; death followed soon afterwards—36 hours after he had been admitted. At post-mortem examination there were solid haemorrhagic patches in the lungs and the trachea and bronchi contained bright pink purulent froth. There was considerable engorgement of the cerebral veins, with moderate flattening of the cerebral convolutions; on section the grey matter appeared pink with diffuse engorgement of the venules certainly not *post mortem* in origin. On microscopy of the brain sections there was no perivascular cuffing and no evidence of encephalitis.

Injection of the throat and eardrums, pallor, and dyspnoea were common findings, but basal rales and harsh breath sounds were heard in only six cases at the first examination. However, all the children developed bilateral chest signs later. Three were admitted in coma, one had convulsions, and another, who later died, developed a purpuric rash. Two children developed an apical systolic murmur before death and we also heard similar murmurs in a number of children recovering from influenza during routine examinations in the out-patient clinics. These murmurs proved to be temporary on further follow-up and were presumably due to a transient myocarditis.

### Investigations and Treatment

Investigations were carried out on 9 of the 13 children; four died before any investigations were implemented. The white blood cell count was high (up to 25,000) in five cases and within normal limits in the other four. The haemoglobin level was below 65% in six cases and blood transfusions were given to two children whose haemoglobin levels were 35% and 55% respectively. Lumbar puncture was carried out in six cases, but on each occasion the cerebrospinal fluid was found to be normal, including that obtained from the 11-year-old boy mentioned above. *X*-ray examination of the chest was carried out in nine cases and reported as normal in four; doubtful basal shadowing in two, bilateral basal inflammatory lesions with collapse of one lobe in one, shadowing of the left lower lobe in one, and shadowing of the left mid-zone in one.

It is interesting to note that on subsequent post-mortem examination of one of the children submitted to *x*-ray examination before death the lungs were found to contain large solid haemorrhagic patches throughout the lung fields, although the *x*-ray film showed only doubtful shadowing at one base. Post-mortem examinations were carried out in two cases; both showed solid haemorrhagic patches in the lungs measuring up to 6 cm. across, and the tracheae and bronchi contained blood-stained purulent frothy material. The larger areas of consolidation were associated with recent fibrinous exudate of the visceral pleura. A swab from the lung produced a pure growth of *Staphylococcus aureus* in only one case. The post-mortem appearances of the brain in one case have already been described.

Treatment consisted of large doses of tetracycline, penicillin, and "eucortone" by intramuscular injection for (on the average) five days followed by a further course of oral tetracycline. Four of the severely ill children were given intravenous tetracycline and large doses of penicillin by intramuscular injection on admission, together with nikethamide and oxygen, but all died. Apart from the children who died, all except two responded to the regime described above within two to three days. The two exceptions were given chloramphenicol instead of tetracycline and the temperature then settled within 48 hours. As already mentioned, two of the children had severe anaemias and required blood transfusions. The haemoglobin level was on the low side in four other cases, so oral iron therapy was instituted. The average length of stay in hospital was nine days, although the two children who were given blood transfusions were kept in for a further 10 days.

### Complications

Of the 13 cases admitted to hospital, 5 died, 6 made complete and uneventful recoveries, 1 was left with a hemiplegia, and 1 was left with a collapse of 1 lobe of the lung which we thought was probably an old lesion and present before the onset of the influenza. The child who subsequently developed a hemiplegia was admitted in convulsions with twitching of the left side of the body, which were controlled by chloral. Five days later, however, she developed a flaccid paralysis of the left arm and leg and was unable to talk. She gradually improved and on discharge there was a spastic paralysis of the affected limbs. On subsequent follow-up some improvement had occurred and she was able to talk as well as she ever did before her illness. This case is also interesting in that at one point before the flaccid paralysis developed the child stopped breathing and became pulseless and was revived after being given nikethamide and artificial respiration by the ward sister.

### Discussion

A great deal has been written about the epidemic, and at the time of writing 14 letters, three leading articles, and one detailed report in the Vital Statistics section have appeared in the *British Medical Journal* alone. Contrary to the views expressed by Fielding (1957) at the onset of the epidemic, and in complete agreement with Cantor (1957) and others, we felt that the epidemic was anything but mild, especially when it attacked children, and more so in children with a pre-existing illness.

Generally speaking, the symptoms and signs described by us are in agreement with those described by others (Atkinson, 1957; Mann and Pasha, 1957; Vital Statistics, 1957). Unlike Atkinson, however, who reported shivering, severe sweating, headaches, and muscular pains as symptomatic of the illness in adults, we did not find these in the children who were admitted to hospital, although severe sweating was noted as a terminal event in two cases. One of us (J. D. P.), however, found headache and muscular pains common presenting symptoms in children seen on domiciliary visits. We were impressed by the paucity of physical signs in the chest, as were Atkinson and Mann and Pasha. We found that the highest death rate amongst children took place in those aged 8 to 14, as was stated in Vital Statistics (1957). We also found that in the fulminating cases with a short history the children succumbed despite the most energetic treatment. We were also impressed by the varying incidence of complications following an attack of influenza in adjoining towns despite the fact that the number of cases of influenza was more or less comparable.

### Summary

The symptoms, signs, and complications, together with the investigations and treatment carried out, are described in 13 cases of influenzal bronchopneumonia occurring in children. The disease was characterized by its sudden onset, its rapid progression, and the paucity of physical signs in the chest. Deaths amongst the children we saw were most common in those aged

8 to 14. The post-mortem findings in two cases are described. Two deaths occurred in previously healthy children and three in children with a pre-existing illness.

We wish to thank Dr. E. L. Simons for the pathological and post-mortem reports.

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# A WOMAN WITH THE STIFF-MAN SYNDROME*

BY

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"A curious condition of progressive, fluctuating muscular rigidity and spasm has recently been described by F. P. Moersch and H. W. Woltman, of the Mayo Clinic, as the 'Stiff-man' syndrome." These were the opening words of an annotation in the *British Medical Journal*† that I was reading in January, 1957, when I realized they were a clear description of the case of a woman whose extraordinary spasms had puzzled me ten years previously. Luckily my ward sister remembered her name; the notes were traced and revealed that the lady had continued to suffer from "hysterical spasm" which had disabled and deformed her till she had become a bedridden cripple cared for in Leamington Park—a geriatric annexe to the Central Middlesex Hospital. Dr. A. Abdullah, the physician in charge, kindly allowed me to review her case. Everything fitted the description in the annotation, and later the annotator himself came and agreed that this woman had the stiff-man syndrome.

I wish to report this case (*a*) because I made the diagnosis ten years late; (*b*) because it appears to be the first case of stiff-man syndrome reported in England; (*c*) because it shows that syndromes are sometimes labelled hysterical for no better reason than that they are not yet officially described, even in this case where the patient's hysterical spasms were so titanic (and that is not a misprint for tetanic) that with their power she bent a Smith-Petersen pin and fractured a steel plate and screws; (*d*) because it shows the value of annotations in keeping physicians in touch with rarities and novelties; and (*e*) because since I recognized the diagnosis the patient has died and the necropsy findings are now known.

## Case History

A housewife of 50 was admitted to hospital in May, 1946, with painful spasms in her legs, abdomen, and back which had been present for two days. She gave a history of "lumbar fibrositis" for six years, treated at another hospital with physiotherapy, and for three years had had increasing back stiffness, which confined her to the house, punctuated by acute attacks of "cramps" in the abdomen, legs, and back similar to the one which brought her in.

Examination showed a dull-witted, distraught woman who groaned continually. The muscles of her abdomen, thighs, and calves were rigid and hard. Her whole body was so stiff she could scarcely move. At intervals acute spasms would come on her with tetanic severity. She would scream and sweat, clutching bystanders, contorting her limbs, and becoming pulseless for a while.

Apart from a generalized rigidity and these remarkable muscular spasms there were no findings except for a colostomy which had been done for ulcerative colitis eight years previously. She had had no bowel troubles since.

She stayed in hospital a month. Every relevant (and irrelevant) biochemical and radiological investigation was negative. Her spasms gradually became less and she was discharged on June 11. I wrote to her doctor, "I am unable to make a definite diagnosis in this case." I made an indefinite diagnosis of spasms secondary to spinal arthritis with hysterical overlay.

Two years later she was admitted to a mental hospital with depression and "troublesomeness." The latter was shown by attacks of spasm and screaming. A month after admission she felt her femur snap during a spasm. The *x*-ray film showed a subcapital fracture of the neck and she was transferred back to the Central Middlesex Hospital, where a 3½-in. (9-cm.) Smith-Petersen pin was inserted. The notes record that next day she was "very troublesome with emotional crises" and subsequent *x*-ray films showed gross varus deformity with bending of the pin and a pertrochanteric fracture through the pin track.

The pin was removed and a mail plate inserted. Again her troublesomeness continued, the deformity recurred, and the screw and plate were broken. A third operation was done two weeks later, but gradually the gross adduction deformity of the right hip recurred. Many attempts were made to mobilize her, but they provoked further spasms and screaming. She developed increasing varus deformity of the feet and her rigidity became worse than ever. She became a chronic case and stayed for five years in the wards before being discharged to a geriatric annexe.

In May, 1955, she was readmitted to the Central Middlesex Hospital for assessment. The houseman's note was: "Condition worsening. Hysterical outbursts on little or no provocation—hyperpnoea, rolling up eyes, clutching fiercely at bed, locker, or bystanders, voluntary rigidity of muscles with opisthotonos, becoming worse if soothed, gradually quietening if ignored."

I was asked to see her, and wrote: "I am most interested to see this woman after nearly ten years. Her condition seems very much the same as when I last saw her. I still feel there must be an organic basis for her symptoms—a sort of dystonia musculorum deformans but without movement."

A psychiatrist was later called, and wrote: "Whatever her difficulties are she appears to be completely lacking in insight and therefore psychologically inaccessible. It is obvious that her rehabilitation is a formidable proposition; she appears to have satisfied some emotional need in her illness. I do not think that any psychiatric approach is likely to be effective and that her treatment is mainly one of general management. I feel the prognosis is bad."

The deformity of the feet induced by constant spasm had now produced a gross talipes equinovarus. This was partially corrected by manipulation and plaster, and while in plaster she succeeded in walking a little with a stick, but when the plaster was removed the deformity recurred, so in November, 1955, an arthrodesis of the left ankle was done and further attempts to mobilize her were made. These achieved little success, so she was transferred to Leamington Park, where they continued for another six months to try to get her up. All efforts at salvage were abandoned finally in August, 1956, when the house-physician wrote: "Very difficult and uncooperative. Prefers to stay in bed. As this makes it much easier for sister and as the patient obviously does not want to get better, it is time we realized we have lost this battle."

Thereafter she remained bedridden—rigid and deformed but moderately content, provided she was not moved, when "hysterical" spasm would recur.

Four months after therapeutic defeat had been openly admitted I visited her again because I had read the annotation mentioned above. The many tattered pages of notes

*I cannot avoid the paradoxical title; those who named this illness called it "stiff-man syndrome"—stiff-person syndrome might be a better name.

†*Brit. med. J.*, 1956, **2**, 1478.

were re-read and condensed and physical examination was repeated. The story outlined here was typical of the syndrome described by Moersch and Woltman, and physical examination was as unrevealing as it had been in their cases.

All there was to find was a hypertrophy of the muscles of the neck and trunk with board-like rigidity of these muscles, the abdominal muscles, and the muscles of the lower limbs. The legs were contorted into grossly misshapen deformities, one ankle had varus of such degree that the sole of the foot was facing upwards.

The urine occasionally revealed a trace of glucose which 4 out of Moersch and Woltman's 14 cases had shown.

To be able to identify and name the condition gave the patient no benefit whatever. No doubt, had she known Matthew Arnold's lines she might have expressed the same wish as he did:

> Nor bring to watch me cease to live
> Some doctor, full of phrase and fame,
> To shake his sapient head and give
> The ill he cannot cure—a name.

With Dr. Abdullah's kind permission the patient was brought over to one of this hospital's weekly clinical meetings at the beginning of January, 1957. When I exposed her body and gently moved one limb to show the muscular rigidity this provoked such dramatic and widespread spasm that she was clearly in great agony, crying out loudly, gripping bystanders till her nails dug into them, and sweating visibly and profusely. It appeared that the one-mile ambulance journey had brought her to a climax of acute spasm, and the nurses who accompanied her begged that she might be given morphine for the journey back. We at the meeting felt guilty that a clinical demonstration had unintentionally produced so much suffering. She returned to Leamington Park under heavy sedation and recovered in a few days. In April a course of "tolseram," 1 g. t.d.s. gradually increasing to 3 g. t.d.s., was tried for one month. It made no difference. Thereafter she remained in her usual rigid bedfast condition for another six months, till her unexpected death on June 18. The house-physician's note makes a suitable epitaph: "Commenced 'hysterical turn' at 10.30 p.m. on June 17, 1957, and settled down at 2 a.m. Found dead at 3 a.m." Her hysteria had at least been awarded the posthumous dignity of inverted commas.

### Post-mortem Findings

A complete microscopical examination showed no changes except those attributable to age and atherosclerosis. The only significant changes were in the muscles. These changes, which showed best in the sacrospinalis muscle and hardly at all in the pectoral muscles, were: (*a*) Abnormal variations in the size and staining reaction of the muscle fibres; the swollen fibres were pale and lacking in striation. (*b*) Increase of the connective tissues both collagen and elastic fibres, principally the former. (*c*) Localized areas of atrophy and fibrosis of muscle accompanied by nuclear aggregates and lymphorrhages.

Dr. C. Treip reported that these muscular changes appeared to be primary and not related to any change in the central nervous system. This supports the idea that this illness may be a type of myopathy. Nevertheless it is possible the changes are secondary to spasm or to prolonged bed rest, and the true pathology still remains uncertain.

### Comment

The way I have described this case is a little unorthodox, but I thought it would make it easier to read. Reports of single cases of rare diseases are not usually exciting; this was an exciting and rather fearful case, so I have tried deliberately to describe it in a way that might convey this.

### Summary

A woman of 50 suffered from progressive, fluctuating muscular rigidity and spasms for over 15 years. The spasms caused a fractured leg and broke the steel fittings used to repair it. For many years the spasms were labelled hysterical. Six months before death a diagnosis of stiff-man syndrome was made because of the clear resemblance to Moersch and Woltman's cases. No treatment did any good. She died after a severe spasm, and post-mortem examination showed muscular changes, which suggests this illness is some form of myopathy.

I am indebted to Dr. A. Abdullah for his courtesy in allowing me to follow up this patient in his wards after she left my care; to my registrar, Dr. L. E. Lennard-Jones, for his general assistance; and to Dr. C. Treip for the post-mortem report and the extensive microscopy studies.

# Medical Memoranda

### Two Cases of Bullous Chicken-pox

Though bulla formation is mentioned as an occasional complication of chicken-pox, it is rarely seen. These cases are interesting in that one aroused a transient fear of phenol poisoning and that both made a complete recovery without residual scarring, in spite of the alarming picture which each presented when the disease was at its height.

On August 13, 1956, in a small housing estate in Surrey, where chicken-pox was epidemic, a girl aged 8 years, successfully vaccinated in infancy and with no history of chicken-pox or herpes, was seen at the commencement of what appeared to be a mild attack of chicken-pox. There were about 20 pocks on the trunk and a dozen on the face, scalp, and neck; none on any mucous membranes. Treatment was started with aspirin and local application of 1% phenol in calamine lotion.

When the patient was next seen, three days later (fourth day of illness), there were several large discrete bullae, each overlying the site of a pock, on brow, nuchal region, left axilla, left elbow, upper abdomen, and vulva. These were filled with a turbid fluid, and varied in area from 7 by 5 cm. to 3 by 2 cm. Each was surrounded by a zone of erythema 1 to 2 cm. wide, and the appearance was of a number of localized burns, as from a hot-water bottle. Scattered over the intervening skin were normal pocks in an unexpectedly advanced state of involution.

Though it seemed unlikely, when such a small proportion of treated pocks had proceeded to bulla formation, the possibility was considered that the patient was abnormally sensitive to the low percentage of phenol in the lotion applied or that the percentage had been accidentally increased in the course of dispensing. Local dressing with 0.5% cetrimide cream was substituted and tetracycline administered orally in the hope of reducing septic complications.

The suspicion of phenolic poisoning was renewed on the following day (fifth day of illness), when there was oedema of the eyelids and face sufficient to close the left eye; but there was no oliguria, and the urine was free from protein and normal on microscopy, so the oedema was assumed to have arisen by drainage from tissues surrounding the large bulla in the left frontal region. There was similar oedema of the vulva. By now nearly all the bullae had ruptured and a central pock could be seen in each of the raw areas revealed.

On the seventh day of illness improvement was apparent. Oedema was lessened and the denuded areas were healing without obvious secondary infection. By the end of the second week the patient was ambulant, and at four weeks there remained only two small cicatrices such as may frequently be found after an uncomplicated attack.

On August 26, 13 days after the onset in the first patient, her brother, aged 17 months, developed bullae on both upper eyelids, scalp, thighs, and one finger, with a heavier crop of normal pocks on the trunk than his sister had had. There had been no contact with the first patient from the

onset of her illness, and precautions had been taken against direct transfer of infection.

Owing to scratching, secondary infection of the bullae in the second case was considerable and cardboard arm splints were required. Local treatment with cetrimide cream and systemic tetracycline was maintained, and by the 28th day of his illness he was completely clear. Both he and his sister were afebrile during the period of observation, showed no signs of toxaemia, and had good appetites throughout.

On September 5, 23 days after the onset of the first case and 10 days after the onset of the second case, the mother of these children, aged 28 years, believed not to have had chicken-pox, developed three groups of small soft bullae on the flexor surfaces of the left arm, forearm, and wrist, and one on the right forearm. These bullae were about 1 cm. in diameter except that on the wrist, which was 2 by 3 cm. There were no other bullae or pocks and no systemic disturbance. The lesions responded rapidly to soaks of 1 in 2,000 potassium permanganate, and by September 24, 19 days after their appearance, they had healed completely.

The mother believed that these lesions had arisen from contact with those of the second case, as they occurred on those parts most closely in touch with him when she held him in her arms for the frequent nursing attention required, and the appearance was certainly more that of a direct inoculation than a systemic infection.

Throughout the present epidemic no similar case has been reported from this small housing estate or from a larger one near by.

The second of the cases described was cared for by my colleague, Dr. Phyllis Phipps, during my absence on holiday.

D. M. KELLETT CARDING, M.B., M.R.C.S.,
General Practitioner, Dorking.

## A Case of Paget's Disease of the Patella

Paget's disease is by no means unknown in the patella, but in almost all cases in which it has been reported in this situation the disease has been widespread throughout the skeleton. This was so in the cases reported by Packard *et al.* (1901), Sugarbaker (1940), and Gutman and Kasabach (1936). The largest series referred to was that of Dickson *et al.* (1945), who found involvement of the patella in only 4 cases out of 367. The present case is of interest in that the disease process was confined to one knee-cap.

### CASE HISTORY

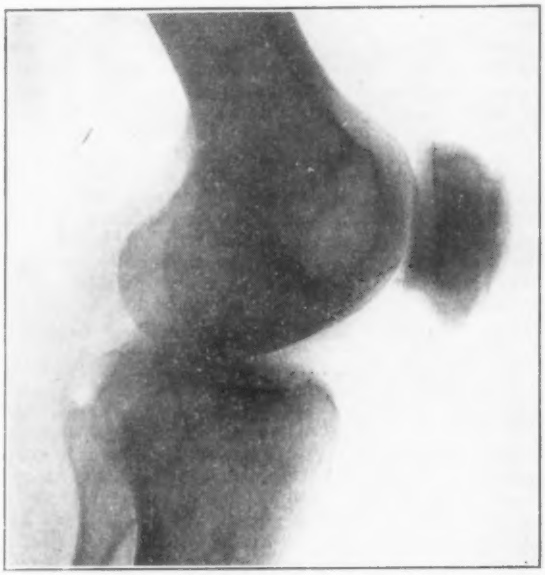
The patient, a man aged 46, complained of aching pain in front of the left knee for three and a half months. There was no history of injury, and the pain, of gradual onset and at first intermittent, had become progressively more troublesome.

On examination, the left knee was found to be warmer than the right. There was palpable enlargement of the left patella, but the knee was otherwise strikingly normal. *X*-ray examination (see illustration) showed a hyperplastic reaction in the patella, and a tentative diagnosis of Paget's disease was made. There were no symptoms related to the other limbs, trunk, or skull, and *x*-ray films showed no lesion in any other part of the skeleton.

At operation on May 3, 1955, the left knee-joint was opened by a medial parapatellar incision. The naked-eye appearance of the interior of the joint, including the articular surface of the patella, was normal. The patella was excised and the extensor mechanism repaired with mattress sutures of No. 30 linen thread, overlapping the ligamentum patellae over the quadriceps tendon. The limb was treated in plaster in extension for six weeks, the patient walking in the P.O.P. from two weeks after operation. Exercises were started out of plaster on June 22, and by the end of August the patient had a fully mobile, strong painless knee.

The excised patella was submitted to Dr. J. E. Morison, of the Belfast Central Laboratory, who reports: "There is very active osteoclastic absorption with numerous multinucleate osteoclasts. In other areas there is very active deposition of bone, and osteoblasts are prominent on the bone trabeculae. Ackerman states that Pagetoid mosaic bone can occur in polyostotic fibrous dysplasia. I suppose it could also be expected to occur in monostotic fibrous dysplasia, but I think there can be little or no doubt that the appearances are those of Paget's disease. In no other condition is there such widespread absorption and deposition of bone within localized areas."

The sections have also been examined by Professor R. A. Willis, who writes: "Although the mosaic pattern is not very prominent, the lesion is probably Paget's disease. I do not know of any record of this being confined to the patella."



Lateral view of the affected knee before operation.

*Comment.*—I have not been able to find a reference in the English or American literature to a case of Paget's disease confined to the patella. The present case is therefore distinctly unusual even if we concede that other parts of the skeleton in this patient may become affected in the future. Little is known about whether, or how, Paget's disease spreads from one area of the skeleton to another. Is it a disease of multicentric origin? Or does it spread directly from a single original focus? Has the removal of the only evident focus in the present case entirely eradicated the disease in this patient? Prolonged follow-up may answer the last question and provide a single shred of evidence towards answering the others.

In the meantime this case provides a most unusual example of the distribution of Paget's disease with a gratifying local and functional result following surgical treatment.

[Since this paper was submitted for publication the patient has died from an unrelated disease (coronary thrombosis). There was no opportunity for a post-mortem examination or the proposed long-term follow-up.]

I wish to thank Mr. R. J. W. Withers for permission to publish this case, and Dr. J. E. Morison and Professor R. A. Willis for their opinion on the sections.

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# Reviews

## DIAGNOSIS AND TREATMENT OF INFECTIONS

*The Diagnosis and Treatment of Infections.* By D. Geraint James, M.A., M.D.(Cantab.), M.R.C.P.(Lond.). (Pp. 234+viii. 30s.) Oxford: Blackwell Scientific Publications. 1957.

This is a book on new lines. It is divided into three parts, of which the first, which might logically have been the second, is a description of the properties, antimicrobic activity, and pharmacological behaviour of antibiotics and some other chemotherapeutic drugs. The second contains accounts of the principal pathogenic micro-organisms and of laboratory methods used in diagnosing infections due to them. Much the largest of these chapters deals with viruses, and will be found helpful by many whom recent advances in diagnostic virology and the advent of such new entities as Coxsackie, ECHO, and A.P.C. viruses may well have bewildered. The third section deals with infections by systems, with some reference to their clinical features and an account of methods for their treatment with antimicrobic drugs and for immunization against them, when either of these proceedings is feasible. Two brief concluding chapters are on diagnosis in P.U.O. ("U" is translated as "unknown," but some people prefer "uncertain") and on the use of corticosteroids in infections.

A very helpful feature is extensive tabulation: anyone who has attempted this will know how difficult it is to secure all the data necessary to complete a really informative table. An example is Table 5, which states, among other things, the amount of each of the principal antibiotics which enters cerebrospinal fluid and the degree to which they are concentrated in the bile. The addition of some tables stating degrees of bacterial sensitivity in quantitative terms would be helpful. It would also be helpful to define all units for antibiotics so measured, and the statement that antibiotics are not amoebicidal needs qualification: oxytetracycline could not exert the effect it does if its action were only on secondary bacterial invaders. Where policy in the use of antibiotics is disputable, the suggestions made will commend themselves, particularly for the treatment of possibly resistant infections and for delaying the emergence of bacterial resistance, although whether some of these measures will actually succeed remains to be proved. It is no small achievement for one author to have so adequately covered both the clinical and the theoretical or laboratory side of this subject, and his book should prove a valuable guide in both diagnosis and treatment.

L. P. GARROD.

## OUTLINE OF NEUROPHYSIOLOGY

*Physiology of the Nervous System.* By F. Geoffrey Walsh, M.A.(Oxon.), M.D.(Harvard), M.R.C.P.(Lond.). With chapters on Somatic Sensibility and the Applied Physiology of Pain by John Marshall, M.D.(Manchester), M.R.C.P., D.P.M.(Lond.). (Pp. 563+xvi; illustrated. 50s.) London, New York, Toronto: Longmans, Green and Co. 1957.

Dr. Walsh in 12 chapters gives a good outline of modern neurophysiology. Two of these are written by Dr. J. Marshall—one on somatic sensibility and the other on the applied physiology of pain. The other ten chapters discuss nerve and muscle; spinal cord; posture-labyrinth; cerebellum; cerebral cortex, olfaction, and electroencephalography; auditory system and temporal lobes; visual system; control of movement; sensory pathway and parietal lobe; hypothalamus, rhinencephalon, and frontal lobes. It is stated in the preface that the intention of this book is to fill the gap between the physiologist on the one hand and the clinician and psychologist on the other. This intention is achieved by making full use of disease entities in illustrating physiological findings, and in presenting excellent accounts of the physiology of the special senses and emphasizing the importance of the latter in interpreting symptomatology and disordered perceptions. For example, in the chapter on hearing Dr. Walsh draws attention to information obtained from diverse disciplines such as that coming from telephone laboratories. From the point of view of the honours student of physiology the text covers the subject in breadth but not in depth. However, the insertion of an up-to-date and extensive bibliography of some 1,200 references gives the opportunity for more detailed studies of recent literature. One omission noticeable is the lack of any detailed description of the reticular formation. Since studies on this aspect of brain physiology derive mainly from countries outside the British Isles, this is perhaps understandable though regrettable.

This book should be of interest to all physiologists, medical students, and clinicians. It is well produced, amply illustrated, and contains, as mentioned above, a full bibliography.

G. W. HARRIS.

## RADIOGRAPHIC TECHNIQUES

*Positioning in Radiography.* By K. C. Clark, M.B.E., F.S.R. Seventh edition. (Pp. 655; illustrated. £5 5s.) London: Ilford Ltd. William Heinemann (Medical Books) Ltd. 1956.

The seventh edition of this work well maintains the high standard set by previous editions and incorporates the latest developments in radiographic techniques. The sections on the various branches of angiography are admirable, and the applications of macroradiography are well set out in that section. Because of the increasing complexity of radiographic techniques, the new edition has been increased by over 100 pages and 600 new illustrations have been introduced, making the total over 2,000. Altogether this is a superb production, one which should be in the hands of every radiologist and radiographer. It has no equal in its field, and the author and publishers are to be congratulated on producing what is a credit to the radiography of Great Britain.

S. COCHRANE SHANKS.

## PIGMENTATION AND VITILIGO

*Dyschromies et Vitiligo: Leur Traitement.* By Edwin Sidi, J. Bourgeois-Spinasse, and P. Planat. (Pp. 142; illustrated. 2,300 fr.) Paris: Expansion Scientifique Française. 1957.

This excellent monograph deals with anomalies of pigmentation and depigmentation. It opens with a clear description of the physiology of pigmentation, which includes the latest work from the whole of the world literature. There are concise accounts of the aetiology, pathogenesis, and clinical pictures of various forms of pigmentation and of vitiligo. The authors' wide experience gives authority to their account of the treatment of vitiligo with *Ammi majus*. They report 11% of patients completely repigmented and 62% partially so, but they also draw attention to their failures and therapeutic accidents. The monograph is beautifully produced and is illustrated by first-class black-and-white pictures. I would particularly draw attention to Fig. 5, which shows a perfect result from the treatment of freckles by abrasion.

F. F. HELLIER.

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The *Medical Annual* has provided an invaluable review of medical progress every year for three-quarters of a century, and the 1957 edition (John Wright and Sons, Ltd., 38s. 6d.) continues the same useful function. From "Abdominal Surgery, Miscellaneous" to "Zoxazolamine" the contributions range over all the subjects on which a clinician might want the latest information. Once again the editors, Sir Henry Tidy and Professor R. Milnes Walker, have commissioned a number of special articles which are much more than mere summaries of recent work. Dr. A. S. Douglas, for instance, explains the modern theory of blood coagulation in a most comprehensive article; Dr. T. Cecil Gray describes the uses of hypothermia; Professor Leslie J. Harris covers much ground in his article on nutrition; and Mr. E. W. Riches writes very clearly and informatively about prostatic enlargement. As usual, the illustrations, especially those accompanying the surgical articles, are excellent, and it is a comfort to see that the publishers are able to sell the book at the same price as the previous edition.

BRITISH MEDICAL JOURNAL
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## CARCINOMA OF THE BREAST

To-day in England and Wales there are probably about 25,000 cases of carcinoma of the breast, which means that every family doctor has, on the average, at least one of these cases to look after in his practice at any one time. The problem is thus of ever-present concern to the doctor, and he may well wonder whether it has changed during the last ten years, whether newer methods of treatment have supplanted the old, and what the outlook for these patients is to-day compared with yesterday. Broadly, it may be said that the standard methods of treatment in vogue ten years ago are still the best, and the outlook for these patients has only slightly improved during the last fifty years.

Since 1942 there has been much controversy over the treatment of the early case,[1] for which radical mastectomy has been the standard operation for half a century. As a result of work in the Edinburgh school a new method of treatment has been proposed for these cases, and it is claimed that this treatment is equally effective in saving life, but does not lead to the troublesome complication of swollen arm. It consists in a simple mastectomy followed by irradiation to the lymphatic fields. The theoretical argument in support of this less mutilating procedure is open to question, and, as no properly controlled series has been investigated, the matter might still be regarded as *sub judice*. However, the weight of evidence seems to indicate that the Edinburgh method, if we may call it that, has not succeeded in establishing itself. Nevertheless, the difference in survival rate between the two methods is not such as to persuade a student of the figures that radical mastectomy must undoubtedly be the better treatment, so that it will probably be only after some years of carefully controlled inquiry, inquiry which has only recently been started, that this vexed question will be finally settled. Meanwhile it is usually a prudent course to adhere to the well-tried and trustworthy methods until the new have proved to be better.

[1] McWhirter, R., *Brit. J. Radiol.*, 1955, **28**, 128.

By contrast, some surgeons have sought to extend the field of operation so as to include the supraclavicular glands and the mediastinal chain. Again, no properly controlled series is available for study, but similar evidence persuades most surgeons interested in these problems that the extended radical or "super radical" operations, as they are called, are unlikely to increase survival rates, will probably increase mortality, and sometimes cause much disfigurement. For these reasons many surgeons conclude that the standard operation of radical mastectomy is probably still the best treatment in the early case. This is not to say that simple mastectomy has not a place in the treatment of this disease. Simple mastectomy is of great value is relieving patients of an offensive lesion when the case has progressed beyond the help of curative ablation. It is sometimes practised for Paget's disease of the nipple when no lump is palpable, but it is doubtful whether this is desirable; it might be argued that, if radical mastectomy is indicated in the early case of established cancer, it is equally indicated in Paget's disease, for there can never be a guarantee that the axillary glands have not become invaded. Simple mastectomy under a local anaesthetic may also be indicated in the elderly or in patients otherwise unfitted for a general anaesthetic.

The prognosis for recurrence after such methods of treatment is much the same as it was fifty years ago, when radical mastectomy first became widely practised. The prognosis for survival is, however, now somewhat better, because life may be prolonged by the administration of hormones in cases of hormone-dependent cancer. The five-year survival rate in patients who are found after radical mastectomy to have no deposits in the axillary lymph nodes is approximately 75%; when the axillary nodes are involved the five-year survival rate is approximately 50%. For the ten-year survival rate these figures are reduced to approximately 60% and 25%.

Certain problems in the management of these cases constantly appear. The first concerns the advisability of performing oophorectomy as a prophylactic against recurrence in women with cancer of the breast who are premenopausal. Some evidence has been adduced which indicates that the survival rate might be improved by this means in young women. But the difference between those who have had oophorectomy performed and those who have not is not sufficiently striking to demand that it should always be done without considering other features of the case. While as a rule oophorectomy may usually be advised for premenopausal patients, it is worth remembering that these patients have already had a

great deal to contend with, and the addition of oophorectomy, with all its psychological and physical burden, may sometimes be too high a price to pay for such a small return. Much the same arguments apply to the possibility of pregnancy in women who have undergone radical mastectomy for carcinoma of the breast. Ideally, for such women to become pregnant is imprudent, but then pregnancy is often to some extent imprudent and there are those women for whom the possession of a baby of their own is the realization of all that they live for; to deny such a woman this joy may be to assume too heavy a responsibility. When, on the other hand, the patient already has children and does not desire to have any more, then the prevention of pregnancy or its early termination if it has occurred is a wise course. In any event, a woman who has had a radical mastectomy for carcinoma of the breast should be advised against becoming pregnant until three years have elapsed and she appears to be free from the disease.

Advances in *x*-ray therapy during the last twenty years have not changed the indications for its use, nor, unhappily, have they affected the ultimate prognosis. What they have done is to make radiotherapy far less obnoxious by delivering the radiation at greater strength and so cutting down the dose to the skin in relation to the deep tissues. There is still some argument about the place of radiotherapy in the early case. Some prescribe it in all cases as a routine before operation, and some prescribe it postoperatively only in those cases in which the axillary glands have been found to be invaded in the operation specimen. There is not much, if anything, to choose between the results of these two schools of thought, but the fact that, when they find a lump in the breast, women tend in this country to report at a much earlier stage than they did twenty years ago means that a far higher proportion of cases need to have the lump removed for inspection and perhaps histological assay before a certain diagnosis can be made. If routine radiotherapy is applied to all cases before operation, then a number of patients will be subjected to this unnecessarily and a few may even have their breasts removed for what may have been an innocent condition.

All are agreed that radiotherapy should be given to patients whose growths are so far advanced as to be inoperable and when they are not too widely disseminated. In this group the prescription of androgens for premenopausal and menopausal women, and of oestrogens for post-menopausal women, has, particularly for the latter, led to a prolongation of comfortable and worth-while life in many cases. In the last resort, the operations either of adrenalectomy with oophorectomy or of hypophysectomy may be considered. In about a third of the patients beneficial results are achieved, and there is not much to choose between these two operations. Some brilliant results have been obtained with both adrenalectomy and with hypophysectomy, and if, as is possible, hypophysectomy is slightly the more effective measure, it must be emphasized that good results with it require exceptional skill and elaborate organization.

## HORMONES AND LIVER DISEASE

The predominant role of the liver in the inactivation of hormones might be taken as *a priori* evidence that liver disease would be associated with endocrine abnormalities. In practice, however, this is seldom the case. Moreover, if a clinical association exists, it has not yet been proved that there is a direct causal relationship, as was emphasized at a meeting last week of the Section of Endocrinology of the Royal Society of Medicine. Nevertheless it is important to bear in mind the possibility of hormonal imbalance, since many of the modern views on the diagnosis and treatment of liver disease are based on such a hypothesis.

While the experimental endocrinologist recognizes that hormonal excess or deficiency causes profound alterations in metabolic processes in the liver, attempts to define specific hepatic changes in endocrine disease in man—for example, in diabetes mellitus and thyrotoxicosis—have generally been unsuccessful.[1 2]


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Certain rare diseases such as Mauriac's syndrome,[3] in which the liver is enormously enlarged, may have such a hormonal basis, and the important observations of J. Gillman and C. Gilbert[4] suggest an association between the fatty liver of severe malnutrition and an imbalance of insulin, adrenal steroids, and thyroxine. How far these findings can be applied to the general problem remains to be seen; they do indicate, however, a fresh approach to the pathogenesis of at least one common variety of liver disease—namely, alcoholic cirrhosis.

Of more immediate interest is the possibility that certain clinical manifestations of chronic liver disease may have an endocrine basis. Patients with portal cirrhosis, especially when it is associated with alcoholism, frequently exhibit characteristic skin changes—spider naevi, palmar erythema, and curious white spots on the buttocks—which are also seen in pregnant women. High levels of oestrogens are found in pregnancy, and these hormones dilate the endometrial arterioles, which have a similar structure to the spider naevus. The liver is known to inactivate oestrogens by conjugation with glucuronides, and attempts have been made to detect impaired powers of inactivation in liver disease. These have not always been successful, probably because of the inadequacy of present analytic techniques, but high levels of oestrogens in the urine have been reported,[5] and the ability to metabolize injected oestradiol is impaired in some patients with cirrhosis.[6] Nevertheless, it is not possible to correlate the skin changes with levels of oestrogen,[6] and there are certain observations which are difficult to explain on the assumption of such an association. While spider naevi can be produced by the administration of female sex hormones,[7] they are not seen in patients with carcinoma of the prostate receiving large doses of stilboestrol. In addition, it is difficult to see how a purely hormonal mechanism could account for the well-known predilection of spider naevi for the upper half of the body. Apart from the skin changes there are a number of inconstant features of chronic liver disease which can be due only to hormonal imbalance. Men occasionally develop gynaecomastia, as well as testicular and prostatic atrophy, while amenorrhoea is not uncommon in women. Loss of libido, infertility, and changes in the distribution of body hair occur in both sexes.

The one constant biochemical finding in severe liver disease is a diminished urinary excretion of 17-ketosteroids,[6 8] and it has been suggested that this is secondary to suppression of pituitary gonadotrophins. The latter could result from the combined effects of malnutrition and oestrogen excess on the anterior pituitary, and such a dual mechanism might explain the more frequent occurrence of hormonal changes in patients with alcoholic cirrhosis, as well as their inconstancy in liver disease in general. Lastly, there is the rather unusual group of young women with chronic hepatitis, in whom signs of adrenocortical overactivity occur.[9] In these patients, the history is one of mild jaundice and dyspepsia, insidious in onset and usually overshadowed by other features such as depression, severe acne, mooning of the face, retention of fluid, and the development of hirsuties and striae. In addition to extremely high levels of gammaglobulin, suggesting some type of immunological reaction, adrenal glucocorticoids are said to be increased, and the tolerance for steroids is impaired. Prognosis is nearly always more favourable than the degree of damage to the liver cells would indicate. It is not yet clear whether this is a separate disease or a manifestation of infective hepatitis in a particular age and sex group. The latter seems the more likely possibility, since there is often a previous history of hepatitis.

An important problem of portal cirrhosis, still unsolved, is the way in which ascites is produced. Portal hypertension presumably dictates the site where the fluid accumulates, while reduction in the level of serum albumin, by lowering colloid osmotic pressure, may also be an initiating factor. It is thought, however, that the perpetuation of ascites is determined by the intense and generalized retention of sodium that results, and that this in turn is maintained by the increased activity of certain endocrine glands. Increased amounts of the salt-retaining hormone aldosterone, for example, have been found in the urine of patients with ascites[10]; this could be due either to excessive production or to defective inactivation by the liver. It has led clinicians to consider bilateral adrenalectomy in such cases, and two patients with intractable ascites who were submitted to operation have been reported in the literature.[11 12] There was some improvement, especially of sodium excretion, but ascitic fluid continued to form, and it was necessary to carry on treatment with a low-salt diet, ion-exchange resins, and mercurial diuretics. A more recent alternative has been to give the drug amphenone, which is related structurally to the synthetic oestrogens and is a powerful inhibitor of adrenal cortical function.[13] The results in four

patients with ascites due to cirrhosis[14] were somewhat similar to those following adrenalectomy, and, although urinary levels of aldosterone always fell to normal, this was not necessarily accompanied by a rise in excretion of sodium. Amphenone is at present difficult to obtain and it causes disturbing side-effects; in cases of severe liver disease it may precipitate hepatic coma. Yet it may well have a place in the management of those patients in whom ascites is resistant to all other forms of therapy.

Retention of water and salt cannot be ascribed solely to the action of the adrenal cortex. Other hormones—for example, oestrogens—have salt-retaining activity, and these may be present in excess when the liver is damaged. J. R. K. Preedy and E. H. Aitken[15] showed convincingly that oestrogens could influence fluid retention, especially when the hepatic circulation was impeded. Evidence that antidiuretic hormone (A.D.H.) plays a part is more questionable, though increased antidiuretic activity has been found in the urine of patients with ascites.[16] As the cirrhotic liver is able to dispose of A.D.H. normally,[17] any increase in activity must indicate excessive production.

At the Royal Society of Medicine meeting J. Lee and G. W. Bisset reported high levels of A.D.H. activity in blood obtained from the internal jugular vein of some patients with liver disease. Assay methods are extremely laborious and the quantities measured minute, so that a larger series must be awaited before the role of A.D.H. can be assessed.

The value of adrenal steroids in the treatment of liver disease remains to be discussed. It must be admitted that they play little part in the treatment of uncomplicated liver disease, either hepatitis or cirrhosis. Occasionally steroids may be life-saving for patients with fulminating viral hepatitis, and they are worth a trial for patients with hepatitis which relapses. They are also diagnostically helpful in deciding whether prolonged obstructive jaundice is due to intrahepatic cholestasis ("cholangiolitic hepatitis") or to extrahepatic obstruction. In the former, a short course of treatment is usually accompanied by a fall in the levels of serum bilirubin and alkaline phosphatase, with subsequent clinical improvement.[18] A fall may also occur in extrahepatic obstruction, but the serum bilirubin rises again when the steroids are stopped.[19] They appear to have an action on production of bilirubin rather than a direct effect on the obstructing process. Whatever the mechanism, this method should be useful in diagnosing the small group of patients with obstructive jaundice who give rise to clinical difficulty.

## NEUROLOGICAL ASPECTS OF PULMONARY EMPHYSEMA

In 1933 A. J. Cameron[1] described a young miner with severe emphysema who developed failing vision and papilloedema. No evidence of intracranial disease was found, and the ocular features diminished as the pulmonary condition improved. Recent studies of the neurological complications of emphysema have clearly demonstrated that they arise from raised intracranial pressure consequent upon $CO_2$ retention.[2–6] Indeed, the cerebrospinal fluid pressure is raised in normal subjects on breathing high concentrations of $CO_2$. The cause of the rise is not fully understood, but most authors agree that cerebral vasodilatation resulting from hypercapnia plays an important part. (Conversely, hyperventilation causes vasoconstriction and a fall in pressure.) This rise in C.S.F. pressure, which often exceeds 300 and can be as high as 500 mm. of C.S.F., may lead to a variety of cerebral disorders in addition to visual disturbances and papilloedema, such as headaches, psychiatric upsets, drowsiness, and coma. They are most likely to occur in severely emphysematous patients during exacerbations of infection. Ordinarily, the respiratory features are dominant, but errors in diagnosis can easily be made in, for example, new patients presenting in a state of coma or semicoma, in whom the whole range of causes of raised C.S.F. pressure has to be considered. H. O. Conn and colleagues[7] recently reported two patients in whom a mistaken diagnosis of cerebral tumour was made. However, a review of recorded cases reveals that almost all were men over the age of 40 having long histories of chronic bronchitis and emphysema, in whom the neurological features were precipitated by a superadded acute infection or by an episode of right-heart failure. The diagnosis should not be difficult, provided it is remembered; it may be confirmed by the response to treatment and, if necessary, by estimations of blood oxygen and $CO_2$.

Treatment, which aims at reducing the tension of $CO_2$, consists essentially of antibiotics to combat infection, a low-salt diet, mercurial diuretics and digitalis to relieve cardiac failure, and oxygen. All of these can be easily administered except oxygen, which presents peculiar problems. In the early stages of emphysema, hyperventilation compensates for the gradually diminishing effective alveolar surface. With more alveolar destruction and obstructed air-flow, hyperventilation is not enough, and $CO_2$ accumulates in the blood, eventually reaching the point at which the respiratory centre becomes unresponsive to it; the ventilatory response to low blood oxygen, however, is unaffected. In these circumstances, oxygen therapy, by relieving the hypoxia, removes the only stimulus to hyperventilation which

[1] Cameron, A. J., *Brit. J. Ophthal.*, 1933, **17**, 167.
[2] Simpson, T., *Brit. med. J.*, 1948, **2**, 639.
[3] —— ibid., 1954, **1**, 297.
[4] Akerren, Y., *Acta psychiat. neurol. scand.*, 1953, **28**, 231.
[5] Davies, C. E., and MacKinnon, J., *Lancet*, 1949, **2**, 883.
[6] Westlake, E. K., and Kaye, M., *Brit. med. J.*, 1954, **1**, 302.
[7] Conn, H. O., *et al.*, *Amer. J. Med.*, 1957, **12**, 524.

remains, and in consequence respiration is greatly depressed. This in turn exaggerates the severity of the $CO_2$ retention and may lead to coma and death from $CO_2$ intoxication. If this threatens, oxygen must be given either intermittently or by means of a mechanical device which will ensure sustained respiration. Usually, intermittent oxygen therapy is all that is needed to tide patients over a few days while treatment of infection and cardiac failure takes effect. A suitable regime is 5–6 litres of 5% $CO_2$ in oxygen for twenty minutes in each hour, but these patients are often restless, mentally disorientated, and intolerant of interference, so that, whether the oxygen be given by face mask or in a tent, close supervision is necessary. If these measures fail, some form of mechanical respirator must be considered. On the whole, tank respirators have found little favour in this disease, mainly because patients tend to "fight" against them. Probably the most effective machine for those in unrelieved coma is an intermittent positive-pressure apparatus of the Beaver or Oxford type connected to an intratracheal tube. Such treatment can be life-saving, but should not be undertaken lightly, because of the possibility of similar subsequent relapses.

## TUMOURS OF THE GLOMUS JUGULARE

The glomus jugulare appears to have been originally described by G. Valentin in 1840,[1] but its existence was largely forgotten, and indeed denied,[2] until S. R. Guild rediscovered it in 1941.[3 4] There may be one or more of these small ovoid bodies which resemble histologically the carotid body, lying in the adventitia of the dome of the jugular bulb or along the tympanic branch of the glosso-pharyngeal nerve (the nerve of Jacobson) or the auricular branch of the vagus (the nerve of Arnold). Since H. Rosenwasser[5] published in 1945 his report of a tumour considered to arise from the glomus jugulare a considerable number of these tumours have been recorded. Before this tumours almost certainly of similar nature had been reported under other names. F. C. W. Capps in 1944[6] described two cases of haemangio-endothelioma of the middle ear, in which re-examination of the sections some years later showed that they originated in glomus-jugulare tissue, and J. Lubbers in 1937[7] described a patient with a carotid-body tumour on one side and a tumour of similar histology in the middle ear on the opposite side.

The early symptoms of these tumours are usually aural, and this aspect has been reviewed by Capps,[8 9] but they often cause more widespread neurological effects, and occasionally the presenting symptoms may be due to impaired function of the lower cranial nerves. Three recent papers[10–12] have dealt with the neurological manifestations. Tumour of the glomus jugulare is probably the most suitable name, but they are at times called tympanic body tumours, non-chromaffin paragangliomas of the middle ear, or chemodectomas (as they arise in a chemoreceptor organ). Pathologically, they are extremely vascular and are composed of nests of epithelioid cells surrounded by a vascular stroma. They are in general very slow-growing benign tumours, but in three reported cases metastases have occurred,[10 13 14] probably as a result of invasion of the lumen of the jugular veins. The tumours occur in adult life and are about five times as common in women as in men, unlike carotid body tumours, which occur about equally in the two sexes. There is some variation in the clinical picture, probably depending on the position of origin of the tumour in relation to the jugular bulb and on the routes of extension of the tumour, whether into the middle ear or into the posterior fossa or into both at about the same time. E. R. Bickerstaff and J. S. Howell[11] recognize four clinical presentations of these tumours. The commonest is by purely aural symptoms, increasing deafness, tinnitus of a pounding type, and bleeding from the ear in association with coughing and straining. Examination will show an aural polyp which bleeds profusely after attempted removal, or in some cases[15] a small strawberry-like area is seen in the lower posterior segment of the drum. It is important to examine microscopically aural polyps in which unexpected haemorrhage occurs during removal. In two further groups neurological symptoms occur in association with the aural ones, either at about the same time or after an interval of ten years or more. The neurological symptoms are due mainly to lesions of the ninth, tenth, eleventh, and twelfth cranial nerves with, in many cases, a facial palsy in addition. More rarely the tumour extends forwards, damaging the fifth and sixth nerves, and in a few cases there are unilateral cerebellar signs. In the fourth group of cases the neurological symptoms are the presenting ones, though deafness is usually present and the diagnosis may be suggested by the characteristic appearance of the tumour behind the tympanic membrane and confirmed by biopsy through the external auditory meatus. In a minority of cases the tumour extends into the neck and can be felt as a pulsatile swelling high behind the angle of the jaw, sometimes associated with a palpable thrill and bruit. In patients who have unilateral progressive lesions of the lower cranial nerves a glomus-jugulare tumour is a possible diagnosis, and aural examination and radiology will usually confirm the diagnosis if it is present. Kemp Harper[16] has described the radiological appearances of these tumours. In the early stages with only aural symptoms sclerosis of the


[1] Valentin, G., *Arch. Anat. Physiol.* (*Lpz.*), 1840, 287.
[2] Watzka, M., *Anat. Anz.*, 1932, **74**, 241.
[3] Guild, S. R., *Anat. Rec.*, 1941, **79**, Suppt. 28.
[4] —— *Ann. Otol.* (*St. Louis*), 1953, **62**, 1045.
[5] Rosenwasser, H., *Arch. Otolaryng.* (*Chicago*), 1945, **41**, 64.
[6] Capps, F. C. W., *J. Laryng.*, 1944, **59**, 342.
[7] Lubbers, J., *Med. Tijdschr. Geneesk.*, 1937, **81**, 2566.
[8] Capps, F. C. W., *J. Laryng.*, 1952, **66**, 302.
[9] —— *J. Fac. Radiol.* (*Lond.*), 1957, **8**, 312.
[10] Henson, R. A., Crawford, J. V., and Cavanagh, J. B., *J. Neurol. Neurosurg. Psychiat.*, 1953, **16**, 127.
[11] Bickerstaff, E. R., and Howell, J. S., *Brain*, 1953, **76**, 576.
[12] Siekert, R. G., *Arch. Neurol. Psychiat.* (*Chicago*), 1956, **76**, 1.
[13] Lattes, R., and Waltner, J. G., *Cancer*, 1949, **2**, 447.
[14] Winship, T., Klopp, C. T., and Jenkins, W. H., ibid., 1948, **1**, 441.
[15] Magarey, F. R., *J. Laryng.*, 1952, **66**, 321.
[16] Kemp Harper, R. A., *J. Fac. Radiol.* (*Lond.*), 1957, **8**, 325.
[17] Williams, I. G., ibid., 1957, **8**, 335.

mastoid and petrous region is the first change, but tomography may show irregular areas of erosion. When there is extension of the tumour the jugular foramen can be seen to be enlarged in the infero-superior view, and there may be extensive destruction of the petrous pyramid and mastoid. Tomography is of considerable value in demonstrating the extent to which the tumour has destroyed bone.

Treatment of glomus-jugulare tumours is difficult. Though they are usually benign and slow-growing, they are extremely vascular, and when there is an intracranial extension complete operative removal of the tumour is impracticable. In the group with purely aural involvement Capps states that haste in treatment is not imperative, but that, when it becomes necessary, a radical tympano-mastoidectomy is the best procedure. If the tumour recurs, it can be attacked by further surgery or radiotherapy. In cases of intracranial extension of the tumour, radiotherapy has been of value[16,17]; deterioration of symptoms has been halted and signs of distinct improvement noted in the cranial-nerve lesions. At present radiotherapy seems to be the most hopeful treatment for the patients who have an intracranial extension of the tumour.

## LOW VACCINATION RATES

In 1955 slightly more than a third of the babies born in England and Wales were vaccinated in the first year of life. The public were interested in protecting their children against poliomyelitis and diphtheria, but evince their faith in vaccination only when there is a scare of smallpox. A similar state of affairs exists in Scotland.[1] There the vaccination rate varies in the cities and burghs from 82% to 14%, and the counties show similar variation. A group of Scottish medical officers of health have tried to find the reasons for this great variation by a survey of the methods used to induce the parents to accept vaccination for their children; it covered over 70% of the population. This inquiry showed that failure to notify, or vaccination delayed beyond the first year, were not the causes of the low figures. Small authorities were as effective (or ineffective) as the large ones in relation to their vaccination rates. Some of the areas of poor vaccination displayed posters as a means of persuasion, but in general posters were found to be of little value. Neither the efforts of the midwife nor those of the child welfare centre seemed very effectual in promoting vaccination. There were, however, some small "pockets" where vaccination was the accepted procedure. The health visitor and the family doctor (the latter especially in rural areas) were the most effective persuaders; vaccination tended to be low where there was a shortage of health visitors.

The public quickly learn to discriminate between facile propaganda and authoritative pronouncements, and the most successful health education results from the personal and intimate discussions of the doctor or health visitor with the parents. This seems to be especially true of vaccination. The whole history of vaccination has been unfortunate.[2] No procedure has been so bedevilled by administrative interference, though some control was obviously necessary to promote a measure which is important for the public safety, especially in the face of determined counter-propaganda. Its name (from *vacca* —a cow) associates it with an animal not particularly hygienic in its habits, a point seized upon by the anti-vaccinationists, who attempted to frighten the population by depicting the vaccinated as acquiring certain bovine characteristics. The violent recriminations between Jenner and his co-vaccinators did nothing to commend the measure. Besides this, the heavy hand of officialdom aroused revulsion to a measure that was uncomfortable and slightly disfiguring. Vaccination was offered free in 1840 and became compulsory in 1853; certain relaxations were introduced in 1907, and these immediately resulted in a fall in the acceptance rate. The rate has fallen again since all compulsion was removed under the National Health Service Acts. For many years vaccination was closely associated with the Poor Law Board—a body that was intensely disliked—and was the perquisite of the public vaccinators, who were usually the Poor Law doctors. There was much criticism of the way the work was done, and there were a number of official inquiries. In one it was admitted that vaccination was associated with "frequent evidence of unskilfulness, evidences especially discreditable in the case of a country which had taught vaccination to the world." Jonathan Hutchinson, when giving evidence before a Select Committee, stated that arm-to-arm vaccination, not prohibited until 1898, had been associated with the transmission of syphilis.[3] The training in vaccination was given separately from the ordinary curriculum in medical schools. The measure itself, despite the improvements in technique, is still associated with particular dangers—though the most important could be almost eliminated if primary vaccination was undertaken in infancy. Even now it is one of the few measures in medicine for which the Ministry of Health officially sets out the precise procedure.

Yet vaccination remains a protection against a serious disease and can still be acknowledged as "Jenner's incomparable benefaction to mankind."[3] The fear of smallpox is shown by the refusal of many Governments to permit unvaccinated persons to enter their countries. Infant vaccination has much to commend it, for encephalitis is rare in infancy and also after revaccination later in life. Few people who have witnessed the reaction of a large population suffering primary vaccination in adult life as a result of a smallpox scare will deny that infant vaccination is more desirable. Vaccination is typical of many of the unpleasant measures which the doctor must advise, often in the face of strong counter-propaganda. But when the public must be educated to accept these measures no procedure can possibly be as effective as the pronouncement of a trusted family doctor, or a health visitor who undertakes the work for him. It is important that those people who advocate mass crusades for health should understand this simple but often forgotten truth.

[1] *Hlth Bull. (Edinb.)*, 1957, **15**, 70.
[2] Hutchinson, J. R., in *Report of the Ministry of Health for the Year Ended March 31, 1946*, 1947, H.M.S.O.
[3] *English Sanitary Institutions*, John Simon, 1890, London.

# WORKING OF A MOTHER AND BABY UNIT

BY

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It has been recognized for some time now that infants avoid cross-infections if they are nursed in single cubicles, that most infants are better if they remain associated with their mothers, and that it is wise, if possible, to take the mothers into hospital with their sick babies.

Since 1952 the new mother and baby unit in the Royal Aberdeen Hospital for Sick Children has been in action, and this article details some of our experiences in its working. The hospital is the only children's hospital in the only large burgh in the North-Eastern Regional Hospital Board area of Scotland—an area that has about half a million inhabitants and around 120,000 infants and children.

The unit is architecturally in two parts—one wing for twelve mothers and their babies, the other for infants without their mothers, this latter portion being in two suites each of ten cubicles, two containing incubators, which can all be seen from the duty room. Off the corridor joining the two halves are doctors' rooms, a lecture room, a visitors' room, and other accommodation. On the approach corridor are three rooms for the registrars and house-physician. Each room for mother and baby measures 12 by 10½ ft. (3.65 by 3.2 m.) and contains a mother's bed, an infant's cot, a built-in wardrobe, a nursing chair, a weighing machine, and a combined type of bath–basin. By a system of bells and lights the mother can get in touch with the nurses' duty room at any time.

There are two bathrooms for mothers and three toilets, each with hand-basin to encourage hand cleanliness. The mothers' dining-room has small tables. Adjacent to it is a small kitchenette equipped with electric cooker and refrigerator where the mothers may prepare extras such as hot beverages when they wish. Their meals are cooked in the main hospital kitchen. The sitting-room is bright, warm, and comfortable, and has a wireless set and bookcases; a terrace outside can be used in the summer-time; there is a private telephone for use by the mothers.

*Staffing.*—A medical registrar and a house-physician comprise the junior medical staff. The nursing staff for the whole unit includes three sisters, four staff nurses, and 13 nurses in training. We have no difficulties in recruitment of nurses.

## Day-to-Day Care

The day-to-day care and nursing of the babies who are accommodated with their mothers is carried out by the parent in close co-operation with the nursing staff. The mother is responsible for cleaning and tidying her room, for making her own and her child's bed, and for washing and drying crockery used for her own meals.

Bottle feeds are prepared by the nursing staff in a separate milk room, but the mother is expected to boil the teats, warm the feeds, feed the baby, and rinse the bottles after use. The mother carries out the bathing and changing of the baby, and she is responsible to a varying extent for the administration of medicines, and even, after instruction, for the instillation of nose- or eye-drops. Weighing and test weighing are usually supervised.

The duties of the nursing staff are largely supervisory and educative, apart from certain tasks which are not performed by the mother, such as surgical dressings, recording of the temperature and the pulse and respiration rates, the collection of specimens, and the administration of injections. Individual tuition is being continuously given. The mother is shown, if necessary, how to bath the baby, how to care for the skin, how to clothe the child, and numerous other minor points in management. The preparation of the feed is demonstrated when artificial feeding is newly begun, as well as how and why to sterilize teats and bottles. Breast- and bottle-feeding are supervised as necessary. The repeated encouragement and advice from medical and nursing staff do much to make the mothers more confident and contented. A small library in the mothers' lounge contains simple books on infant care as well as a larger selection of fictional and other literature. The possibility of tuition of the mothers by lectures has been considered but has so far not been adopted, the system of individual instruction being thought preferable with a rapidly changing series of pupils.

## Social Questions

*Social Mixing.*—There has been daily visiting in the hospital for the last 10 years at a fixed hour in the afternoon, but the mothers can receive visitors at other times. The fathers often visit their wives in the evenings. The mothers are free to go out at any time, and indeed are encouraged to take some exercise if they are fit—just as they are advised to rest in bed in the afternoon if they are breast-feeding and are feeling tired. Mothers from all social classes come into the ward. Living door to door, conversing together in the lounge, sharing the same table at meals may be the wives of farmers and farm labourers, ministers and parishioners, shipowners and fishermen. Included also are a number of unmarried mothers, and it is surprising how well all these people from varying walks of life and of widely different age and outlook intermingle and share work and worries. The common problem of an ill child provides a very firm bond between the mothers.

*Care of the Home.*—The absence of the mother from a family, however small, causes a large hiatus which may be filled in various ways. The most simple situation is that where the father is not living at home, being at work elsewhere, such as in H.M. Forces or at sea with the fishing fleet, there being a large fishing industry in Aberdeen and the north-east of Scotland. In this circumstance the mother may find admission to hospital a relief from loneliness and monotony. More often the father is left on his own, when he may obtain his meals from neighbours or relatives or may live entirely with them, or, according to his domestic capabilities, he may fend for himself. When children are left at home the situation is more difficult, but there seems to be no lack in most cases of relatives who are willing to accommodate the children. The grandmother is the person who most frequently fills the breach. Quite often, however, the father copes with the situation himself, usually by taking one or more weeks' holiday from his work; alternatively, he may board out the children with relatives or neighbours during the day, resuming his responsibilities again in the evening.

## Survey of Admissions

A brief survey has been carried out of all admissions to the unit since it was opened, the year 1955 being analysed in more detail.

Table I shows the steady rise in total admissions, the increase being due partly to the fact that the unit was not fully functional until October, 1953, but probably also to wider publicity and knowledge of the facilities available. Several mothers were questioned regarding the source from

which they initially learned of the unit, and it was found in most cases that the parents were ignorant of the facilities available until informed at the time of admission by their general practitioner or by the staff of one of the maternity hospitals. A few mothers had noted the press publicity surrounding the opening of the ward or that concerning a visit by Her Majesty the Queen, or had heard broadcasts on the subject in the "Woman's Hour" programme of the B.B.C. Very encouraging is the steady rise in the percentage of babies who are accompanied by their mother, fully one-third now falling into this category.

TABLE I.—*Annual Admissions*

| Year | Total Admissions | Baby Alone | Mother and Baby | |
|---|---|---|---|---|
| | | | No. | % |
| 1952 | 299 | 234 | 65 | 21·7 |
| 1953 | 356 | 265 | 91 | 25·6 |
| 1954 | 524 | 348 | 176 | 33·6 |
| 1955 | 560 | 358 | 202 | 36·1 |
| 1956 | 576 | 367 | 209 | 36·3 |

## Analysis of 1955 Admissions

The total number of admissions to the unit in 1955 was 560, divided into 430 medical cases and 130 non-medical cases, the latter group being mainly surgical. Babies with infantile eczema are usually admitted to a ward with separate cubicles unless the mother is particularly keen to come in with the baby and is prepared for a protracted stay in hospital, but not infrequently these children are admitted in order to give the mother a rest; they are not included in the series.

Of the 430 medical admissions, 155 (36.0%) were accompanied by mother for at least part of the time: 137 babies had their mother with them for the whole period, and 18 for part of the admission. Increasing use is being made of the practice of admitting the mother to the ward for a few days before the baby goes home, especially where there is a feeding difficulty or a nursing problem, perhaps with a technique of surgical dressing or splinting to be learned. Of 108 surgical cases, 30 (27.8%) were accompanied, and 17 (77.3%) of the remaining 22 miscellaneous cases.

The average duration of admissions is shorter in the mothers' end of the ward, so that if we use bed-occupancy as opposed to number of admissions as a guide to the necessary proportion of mothers' beds, we find that we should allow one mother's bed for every 3.5 cots for unaccompanied infants. On the other hand, there is wide fluctuation from time to time in the number of mothers coming in, and it may therefore be advisable to have a slightly higher proportion of mothers' beds.

The type of cases admitted with their mothers may be seen from Table II. The only factors deciding whether the mother accompanies her child are her wishes in the matter and her ability to make arrangements for the care of other members of the family, except that during the puerperium mothers are not admitted until five days after delivery. The cases admitted without mother have not been tabulated but include all the usual reasons for admission of children under 1 year of age.

TABLE II.—*Reasons for Admission of Mother and Baby* (1955)

| | |
|---|---|
| *Medical Admissions* | |
| Establishment of breast-feeding | 42 |
| Feeding difficulty | 35 |
| Pyloric stenosis | 21 |
| Infections | 20 |
| Congenital defects | 7 |
| Prematurity (*per se*) | 4 |
| Hiatus hernia | 4 |
| Investigation of vomiting | 8 |
| Haemolytic disease of the newborn | 4 |
| Miscellaneous | 10 |
| | 155 |
| *Non-Medical Admissions* | |
| Surgical: | |
| Correction of congenital deformity | 11 |
| Herniorrhaphy | 7 |
| Intussusception | 2 |
| Drainage of abscess | 3 |
| Miscellaneous | 7 |
| Miscellaneous (including 6 ophthalmological) | 17 |
| | 47 |

*Geographical Distribution of Patients.*—Comparison has been made between the two sections of the ward—namely, mothers' wing and babies' wing—according to whether the family reside in the City of Aberdeen or in the surrounding rural districts. Table III shows that there is no significant difference between the various groups, mothers from the outlying districts being as willing to come into hospital as those from the city, despite the fact that they cannot visit their homes for short periods during the day, that they have less frequent visits from husband and relatives, and that in view of the relative paucity of social services in the country they must have more difficulty in making arrangements for care of the family at home. For those mothers who bring their infants from the far Orkney and Shetland Islands the unit must be a welcome convenience.

TABLE III.—*Geographical Distribution of Patients*

| | Baby Alone | | Mother and Baby | |
|---|---|---|---|---|
| | City | County | City | County |
| Medical | 148 | 127 (46·1%) | 83 | 72 (46·5%) |
| Non-medical | 53 | 30 (36·1%) | 32 | 15 (31·9%) |
| Total | 201 | 157 (43·8%) | 115 | 87 (43·1%) |

*Age of Patients.*—Table IV shows the total numbers of admissions at various ages in the first year, and the percentages accompanied by mother have been calculated.

TABLE IV.—*Age of Patients*

| Age | Medical | | Non-Medical | | Total | |
|---|---|---|---|---|---|---|
| | Baby Alone | Mother and Baby | Baby Alone | Mother and Baby | Baby Alone | Mother and Baby |
| < 1 week | 57 | 35 | 2 | 1 | 59 | 36 (37·8%) |
| 1 week– | 34 | 58 | 8 | 9 | 42 | 67 (61·5%) |
| 1 month– | 85 | 45 | 23 | 17 | 108 | 62 (36·5%) |
| 3 months– | 38 | 8 | 27 | 9 | 65 | 17 (20·7%) |
| 6 months–1 year | 61 | 9 | 23 | 11 | 84 | 20 (19·2%) |

Apart from the first week of life there is a steady fall with increasing age in the percentage of babies accompanied by the mother until after 6 months the figure is under 20%. The lower figure for the first week is because, as mentioned above, mothers are not admitted during the first few days of the puerperium. The later decline must be partly attributable to the lower percentage of breast-fed infants in the older group, but the difference is largely due to the relatively large number of patients in the early weeks who are transferred from the neighbouring maternity hospital for establishment of breast-feeding or admitted from elsewhere because of feeding difficulty.

*Number of Other Children in Family* (medical cases only).—As would be expected, the mothers with no other live children were most willing to remain with their sick child, but approximately one-third (53 out of 155) of the mothers who were admitted had other children at home (Table V). Of 170 mothers with no other live children, 60% were admitted.

TABLE V.—*Number of Live Siblings (Medical Cases Only)*

| No. of Other Live Children | 0 | 1 | 2 | 3 | 4 | 5 or More |
|---|---|---|---|---|---|---|
| Baby alone* | 68 | 71 | 58 | 30 | 23 | 20 |
| Mother and baby | 102 | 30 | 12 | 7 | 2 | 2 |

* Information not available in 5 cases.

*Age of Mother* (medical cases only).—The medical series of cases has been scrutinized to determine whether either the younger or older mothers tended to come readily into hospital (Table VI). As would be expected, there are fewer maternal admissions in the older age groups where there is an increased likelihood of there being other children in the family. There is no indication of an increased willingness of the elderly primipara to enter hospital with her child:

TABLE VI.—*Maternal Age* (Medical Cases Only)*

| Age of Mother | No. of Cases | |
|---|---|---|
| | Baby Alone | Mother and Baby† |
| Under 20 years .. .. .. .. | 20 | 6 (23·1) |
| 20–24 ,, .. .. .. .. | 81 | 73 (47·4) |
| 25–29 ,, .. .. .. .. | 79 | 44 (35·8) |
| 30–34 ,, .. .. .. .. | 52 | 19 (26·8) |
| 35–39 ,, .. .. .. .. | 28 | 5 (15·2) |
| 40 years and over .. .. .. .. | 7 | 6 (46·2) |
| Total .. | 267 | 153 |

* Information not available in 10 cases.
† Numbers in brackets express percentage of total admissions in each age group.

seven (41.2%) of 16 primiparae over 30 years of age did so compared with 95 (61.7%) of 154 primiparae under 30 years.

*Breast-feeding* (medical cases only).—Of the 275 babies admitted alone, 20 (7.3%) were breast-fed at the time of admission and 8 of these 20 were still breast-fed when discharged home, most of them being city cases where the mother attended hospital several times a day to feed the baby; two others in this group died and eight were artificially fed. In the mother and baby wing 97 (62.6%) were breast-fed on admission and 62 (40%) on discharge. This fall is due mainly to cases admitted as feeding difficulty owing to poor supply, and to failure of establishment of breast-feeding in difficult cases transferred from the neighbouring maternity hospital. Another major cause of failure was found to be pyloric stenosis; of the 21 cases admitted with mother, 15 were initially breast-fed, but the supply failed in hospital in six of these, while a seventh case was only partly breast-fed on discharge and was artificially fed a week later. Thus there was failure of well-established breast-feeding in almost half the cases of pyloric stenosis, a figure not rivalled by any other illness. It is postulated that while maternal anxiety may partly account for this, at least as important is the period of approximately 48 hours during which breast-feeding is discontinued. Failure of breast-feeding was due to:

| | |
|---|---|
| Failed establishment of breast-feeding .. .. .. .. .. | 12 |
| Admitted as feeding difficulty with insufficient milk .. .. .. | 9 |
| Pyloric stenosis, with failure of milk supply .. .. .. .. | 6 |
| Maternal breast abscess .. .. .. .. .. .. | 1 |
| Thrush stomatitis .. .. .. .. .. .. .. | 1 |
| Congenital heart disease .. .. .. .. .. .. | 1 |
| Various diagnoses with failure of supply .. .. .. .. .. | 3 |
| Various diagnoses with breast-feeding discontinued on maternal request | 2 |

*Analysis of Cases Transferred from Maternity Hospital for Establishment of Breast-feeding.*—Forty cases were transferred from the neighbouring maternity hospital during 1955 for establishment of breast-feeding, either premature babies or full-term infants where difficulty had arisen. Twenty-eight babies were premature and 12 full-term. The mothers from the rural districts seemed to be more willing than the city mothers to spend those extra days in hospital, 12 county and 28 city mothers being transferred compared to the total maternity hospital deliveries of 715 rural and 2,670 city patients—that is, 1.7% of all the rural mothers and 1.1% of all the urban mothers. Breast-feeding was successfully established in 20 premature and 8 full-term babies, an overall success rate of 70%. It is felt that this figure is actually higher than it should be, and that perhaps some of the more difficult cases are not being transferred.

### Conclusions

Now that the mother and baby unit has been in use for a number of years, we may survey the advantages and disadvantages. On the credit side there are benefits to the child, to the mother, and to the medical and nursing staff. The child is protected from cross-infection, he is able to continue breast-feeding, and his familiar environment is largely preserved. The mother is able to share the child's illness and to partake of his hospital experience so that when recovery takes place she understands better all that has been involved, and knows that she has played some part in his care. The mothers also learn much about infant management during their stay in hospital, and they benefit from the opportunity to take adequate rest and relaxation. Doctors and nurses, from close contact with the mothers, learn better to appreciate the outlook of the mothers and to understand their worries and problems. We have gained a greater understanding of the social and emotional aspects of medical practice. Difficulties have been surprisingly few: the main ones have been those of ensuring that the home continues to function while the mother is in hospital, and in this respect we have been assisted greatly by our hospital almoner, who meets all these mothers.

As regards the future, we feel that we would certainly wish as at present to continue admitting the mothers of young babies, but at least as great a need is felt for accommodation for mothers of children of pre-school age.

## MEDICAL SCHOOL FOR RHODESIA AND NYASALAND

A medical school should be established at the University College of Rhodesia and Nyasaland, in Salisbury, with the new African hospital at Harari as its teaching hospital. This advice is given to the College by its planning committee in a first report. The committee, which was appointed eighteen months ago under the chairmanship of Mr. L. FARRER-BROWN, director of the Nuffield Foundation, was asked:

"To advise the University College of Rhodesia and Nyasaland on the desirability and practicability of establishing a medical school as an integral part of the College; to prepare proposals for the training curriculum, postgraduate training, the research facilities, the building, equipment, and staffing required, including those required for a suitable teaching hospital, and other centres for clinical facilities; to prepare estimates of the capital and recurrent costs involved and a phased time-table for development; and to make any other proposals and suggestions for the development of medical education and research under the auspices of the College."

The other members of the planning committee, besides the chairman, were Professor W. MELVILLE ARNOTT, professor of medicine, University of Birmingham; Professor T. H. DAVEY, professor of tropical hygiene, University of Liverpool; Professor P. B. MEDAWAR, F.R.S., professor of zoology, University College, London; Professor R. MILNES WALKER, professor of surgery, University of Bristol; Professor A. D. M. GREENFIELD, professor of physiology, Queen's University of Belfast; and Miss HONOR SMITH, reader in medicine, University of Oxford. The committee visited the Federation's three territories last April, and received written and oral evidence from numerous individuals and organizations. The College authorities state that they are now considering the committee's recommendations.

### Need to Build Soon

Not only does the planning committee warn the Federation that it will fall behind other comparable communities "unless it includes a medical school in its plans"; the committee recommends that the school should be established soon. There is a need to train doctors locally, states the committee, and also both the need and opportunity for research. Even if a beginning were made at once, it would be ten years before the first students would become registrable as doctors, as building and the recruitment of staff would take at least three years, and the undergraduate course a further six or seven years.

Stressing the importance of high standards, the committee "regards it as axiomatic that the medical school should provide a course of university standard leading to a qualification which is registrable by the General Medical Council." Such a school, with an intake of 25 students a year, would require a capital expenditure of £1m. and an annual recurrent expenditure of £250,000. Although the committee recognizes the choice of Harari Hospital for the school's teaching hospital as not ideal, as the hospital is seven miles (11 km.) outside Salisbury, this is thought preferable to having the hospital at Bulawayo, some 220 miles (354 km.) away from Salisbury and the College.

## APPROVED NAMES

On October 26, 1957 (p. 995), we printed the last supplement (dated October, 1957) to the consolidated list of "approved names" selected by the British Pharmacopoeia Commission. The new supplement, dated January, 1958, is printed below.

This list is unusual in that it includes 12 synthetic narcotics which fall under international control but are not available as therapeutic agents. These drugs are indicated by the word "Narcotic" in parentheses in the column provided for brief notes on the main use of each drug. Communications relating to "approved names" should be addressed to the secretary, British Pharmacopoeia Commission, General Medical Council Office, 44, Hallam Street, London, W.1.

*Supplementary List*

| Approved Name | Chemical and Other Names | Notes |
|---|---|---|
| Alphacetylmethadol | α-3-Acetoxy-6-dimethylamino-4:4-diphenylheptane<br>*O*-Acetate of α-6-dimethylamino-4:4-diphenylheptan-3-ol | (Narcotic) |
| Alphamethadol | α-6-Dimethylamino-4:4-diphenylheptan-3-ol | " |
| Azacyclonol .. | Diphenyl-(4-piperidyl)methanol<br>"Frenquel" is the hydrochloride | Sedative used in treatment of schizophrenia |
| Betacetylmethadol | β-3-Acetoxy-6-dimethylamino-4:4-diphenylheptane<br>*O*-Acetate of β-6-dimethylamino-4:4-diphenylheptan-3-ol | (Narcotic) |
| Betamethadol | β-6-Dimethylamino-4:4-diphenylheptan-3-ol | " |
| * Bromodiphenhydramine | 2-(4-Bromodiphenylmethoxy)ethyldimethylamine<br>4-Bromo-α-phenylbenzyl 2-dimethylaminoethyl ether<br>"Ambodryl" | Antihistamine |
| Chlorothiazide | 6-Chloro-7-sulphamoylbenzo-1:2:4-thiadiazine 1:1-dioxide<br>"Chlotride"; "Diuril"; "Saluric" | Diuretic |
| Choline theophyllinate | Choline salt of theophylline<br>"Choledyl" | Bronchodilator in bronchospasm with diuretic properties |
| Cyclopregnol | 6β-Hydroxy-3:5-*cyclo*pregnan-20-one<br>"Neurosterone" | Steroid for treatment of certain mental states |
| Cycloserine .. | *D*-4-Aminoisoxazolid-3-one<br>"Seromycin" | Treatment of pulmonary tuberculosis |
| Deserpidine .. | 11-Demethoxyreserpine<br>"Harmonyl" | Tranquillizer |
| Desomorphine | Dihydrodeoxymorphine | (Narcotic) |
| †Dimephetanol | 6-Dimethylamino-4:4-diphenylheptan-3-ol<br>"Methadol" | " |
| Diphenylpyraline | Diphenylmethyl 1-methyl-4-piperidyl ether<br>"Histryl" is the hydrochloride | Antihistaminic |
| Etoxeridine .. | Ethyl 1-[2-(2-hydroxyethoxy)ethyl]-4-phenylpiperidine-4-carboxylate | (Narcotic) |
| Hexocyclium methylsulphate | 1-(2-*cyclo*Hexyl-2-hydroxyphenethyl)-4:4-dimethyl-piperazinium methylsulphate<br>"Tral" | Anticholinergic |
| Hydromorphone | Dihydromorphinone<br>"Dilaudid" is the hydrochloride | Analgesic with morphine-like effect |
| Mannomustine | 1:6-Di-(2-chloroethylamino)-1:6-dideoxy-D-mannitol<br>"Degranol" is the dihydrochloride | Antineoplastic with cytostatic substance |
| Methyldesorphine | 6-Methyl-$\Delta^6$-deoxymorphine | (Narcotic) |
| Metopon .. | Dihydromethylmorphinone | " |
| Myrophine .. | Myristyl ester of benzylmorphine | " |
| Nandrolone .. | 17β-Hydroxy-19-norandrost-4-en-3-one<br>19-Norandrostenolone<br>17β-Hydroxyoestr-4-en-3-one<br>"Durabolin" is the phenylpropionate | Treatment of senile osteoporosis and palliative treatment of inoperable mammary carcinoma |
| Oxycodone .. | Dihydrohydroxycodeinone<br>"Eucodal" is the hydrochloride | Analgesic with morphine-like effect |
| Oxymorphone | Dihydrohydroxymorphinone | (Narcotic) |
| Promazine .. | 10-(3-Dimethylaminopropyl)-phenothiazine<br>"Sparine" is the hydrochloride | Ataractic |
| Proquamezine | 10-(2:3-Bisdimethylaminopropyl)-phenothiazine | Spasmolytic agent |
| Thalidomide .. | α-Phthalimidoglutarimide<br>"Distaval" | Sedative |
| Thebacon .. | Acetyldihydrocodeinone | Analgesic with morphine-like effect |
| Trimeperidine | 1:2:5-Trimethyl-4-phenyl-4-propionyloxypiperidine | (Narcotic) |

* Replaces the approved name bromazine.
† Replaces the approved name methadol.

# Preparations and Appliances

## NEW HEEL PAD FOR PREVENTION OF ISCHAEMIC ULCERS

Dr. A. POTELIAKHOFF, senior medical registrar, St. Mary Abbots Hospital, London, W.8, writes: Ischaemic ulceration of the heels is an infrequent complication in comatose, arteriosclerotic, diabetic, or paralysed patients, but when, in spite of all nursing care, the heels break down, a serious problem arises. As a prophylactic measure a new type of protective heel pad has been devised and found by experiment to be simple in use, time-saving, and effective. It consists of a shaped "sorbo" rubber appliance ¼ in. (2 cm.) thick, perforated for ventilation, which fits the heel and malleoli as shown in the photograph. The outer surface and edges are covered with a thin sheet of rubber to ensure longer life and to allow sliding movements of the foot. The pad is held in place by two 1-in. (2.5-cm.) straps which lie flat against the skin.

The appliance should be used, without loss of time, in all cases of coma, of paralysis of the legs, in bedridden patients with a defective blood supply to the feet, especially if diabetic, and in patients with threatened gangrene. The feet are cared for in the usual way, and after they have been washed, rubbed with spirit, and powdered the heel pads are applied without underlying dressings, except where an ulcer has already formed. Provided the straps are loose, there is no danger of pressure on the dorsalis pedis artery.

To test the efficiency of this heel pad a controlled experiment was carried out in four medical wards totalling 120 beds for a period of six months. In two wards conventional rings were applied as necessary, while in the other two wards the sorbo rubber pads were used as indicated above. Ischaemic ulcers developed in nine patients during that period—four in the group using sorbo pads and five in the control group. In the former group one ulcer was present before admission and one occurred in a woman who was uncooperative and refused at first to wear the pads. She later consented to wear them, and the small ulcer healed rapidly. In two other patients the pads were not put on immediately on admission, and the damage occurred in the short interim period. To sum up, no ulcers occurred in patients in the trial group except if the damage had already taken place before admission or if the pads were supplied too late. In this connexion it is considered that the cutting off of the blood supply to a part for even a short period can result in gangrene. In the control group three, possibly four, preventable ulcers developed. These figures are not large enough to be of statistical significance, but they do support the clinical impression of the usefulness of the pads.

The pads can be cleaned with soap and water and sterilized with antiseptics. With care they will last for over a year and are well worth the moderate initial outlay. They are obtainable from Messrs. John Bell and Croyden, 50, Wigmore Street, London, W.1.

I am grateful to Sisters Bennet, Moyse, Richards, and Whiteford for their valuable co-operation. My thanks are also due to Mr. H. A. W. Bond, of Messrs. John Bell and Croyden, whose advice on the construction of the pads has been of great help.

# Correspondence

## Hypoglycaemia and the Mind

SIR,—I read your leading article on "Hypoglycaemia and the Mind" (*Journal*, January 18, p. 150) with special interest, because many cases with indefinite symptoms for which no obvious cause can be found are referred to me with the diagnosis of spontaneous hypoglycaemia. In the majority, investigation under proper conditions of diet reveals no abnormality in carbohydrate metabolism, and the diagnosis of hypoglycaemia is found to have been made as a result of a failure either to appreciate the limits of a normal blood-sugar curve or the difference between total reducing and absolute glucose values. In this connexion it would be a good thing if pathologists were to state on blood-sugar reports not only the time of day at which the blood was taken but also the method of blood-sugar estimation used.

In my opinion the rather low figures which are sometimes found in patients labelled functional spontaneous hypoglycaemia are usually not responsible for the clinical picture, but only a common finding in association with certain types of emotional disorder, and I have found good psychotherapy sometimes more effective than low carbohydrate diet or buffer meals in correcting the blood-sugar level. Indiscriminate blood-sugar curves are no substitute for a careful history which would have revealed the true cause of the trouble—namely, petit mal—in the last two cases of so-called spontaneous hypoglycaemia who came to see me, complete with the usual bundle of biochemical investigations.—I am, etc.,

London, S.E.5. WILFRID OAKLEY.

## Respiratory Infections in the Family

SIR,—The authors of the paper on "Family Studies of Respiratory Infections" (*Journal*, January 18, p. 119) surely deserve congratulations on an exemplary and painstaking study of a most important subject. As a throat and ear surgeon I was particularly interested in Table XVIII and in the comments on this at the end of the "Summary and Conclusions." Many readers will be left with the impression that the figures prove the futility of tonsillectomy in these cases, at least from the clinical point of view and so far as the disorders listed are concerned.

It seems to me that the reverse can be argued equally well. The children whose tonsils had been removed cannot properly be compared in this connexion with those whose tonsils remained. It is reasonable to suppose that the former group was more liable to these disorders prior to operation than the latter and that it was this increased susceptibility which determined the decision to operate. Is it not a logical inference that tonsillectomy—and/or removal of adenoids, no doubt—had succeeded by rendering these children no more liable to the disorders studied than the erstwhile healthier group in which the question of this operation had not arisen ?—I am, etc.,

London, S.E.1. L. F. W. SALMON.

## Sickle Cells and Salmonellae

SIR,—Your annotation "Sickle Cells and Salmonellae" (*Journal*, December 28, 1957, p. 1537) should stimulate interest in the curious and puzzling association between sickle-cell anaemia and salmonella infections. On reading it I was reminded of a paper by Cuadra[1] in which he records that patients suffering from Oroya fever (the haemolytic stage of bartonellosis) have a peculiar susceptibility to salmonella infections, and it would be interesting to know if there are records in the literature of salmonellosis complicating other forms of haemolytic anaemia.—I am, etc.,

London, N.W.1. W. H. JOPLING.

REFERENCE

[1] Cuadra, C. M., *Texas Rep. Biol. Med.*, 1956, **14**, 97.

## Wheat, Antibiotics, and Intestinal Symptoms

SIR,—The unpleasant gastro-intestinal symptoms which so frequently follow treatment with chlortetracycline, and less frequently with the other antibiotics, have been attributed to many causes. An unsuspected aggravating cause of these symptoms is the eating of wheaten products. I have now observed five cases in whom the eating of bread excited severe cramp and diarrhoea, associated with a sometimes remarkable degree of intestinal flatus. In all cases pruritus ani was also present, but appeared to be unrelated to the eating of bread. The effects of eating wheaten products were related to the amount eaten, and each patient was able to find for himself the amount which could be tolerated. This condition is similar to the intestinal carbohydrate dyspepsia described by Hurst.[1] It is a simple matter to test this possibility as a cause of the symptoms, and one may be able to give the patient complete relief by restricting the amount of bread eaten.—I am, etc.,

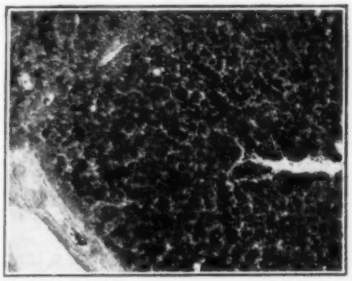
London, N.W.3. J. PEPYS.

REFERENCE

[1] Hurst, A., *British Encyclopaedia of Medical Practice*, 1937, **4**, 370.

## Fatty Liver of Endocrine Origin

SIR,—One of the experiments described by Drs. Joseph Gillman and Christine Gilbert in their paper on the fatty liver of endocrine origin (*Journal*, January 11, p. 57) shows that prolonged treatment of hypophysectomized baboons with cortisone can result in intense fatty infiltration of the liver. This prompts us to draw attention to the finding of a fatty liver in a case of Cushing's syndrome. The case was reported to the September meeting of the Association of Clinical Pathologists.[1] The patient was a woman aged 42 years and there was evidence of great overactivity of both the adrenal cortex and the pituitary. (Daily excretion of 17-ketogenic steroids was 110 mg. and the patient was deeply pigmented.) An operation for adrenalectomy was carried out and it was noticed that the liver appeared abnormal. A small biopsy was taken which on section revealed a very considerable fatty infiltration (see Fig.). There was also a slight but definite increase in the periportal fibrous tissue.—We are, etc.,



Section of liver stained for fat with Sudan IV. The central vein is shown and a portion of the portal area (×50).

P. N. COLEMAN.
A. W. B. EDMUNDS.

Northallerton, Yorkshire.

REFERENCE

[1] Edmunds, A. W. B., McKeown, K. C., and Coleman, P. N., *J. clin. Path.*, in press.

## Plasma-cell Mastitis

SIR,—Mr. B. N. Colabawalla is to be congratulated on his report (*Journal*, December 7, 1957, p. 1352) of a typical case of plasma-cell mastitis which came under his observation. The paucity of cases recorded in the literature to date suggests that this condition is still continuing to pass unrecognized more than a quarter of a century after its original description.

The clinical picture was brought to light by Dr. Max Cutler[1] in 1931 following a study of 10 cases from the records of the Memorial Hospital in New York, and it was sufficiently characteristic to establish the condition as a clinical entity. The aetiology was clarified by Rodman and Ingleby,[2] of Philadelphia, in 1939, who claimed that it was a chemical irritation of the periductal tissues caused by products of lactation which had been retained in the milk ducts of the breast. They were able to reproduce the

histological picture experimentally by injecting pancreatized milk into the breast of virgin rabbits and pancreatic extracts into the breast of lactating rabbits. In 1941, along with Dr. M. B. Dockerty, I[3] reported 24 cases of plasma-cell mastitis from material at the Mayo Clinic. The findings in this study confirmed the accuracy of Dr. Cutler's original description and served to emphasize that the disease occurred only in parous women and frequently in those who for some reason or another had been unable to put the infant to the breast.

The characteristic clinical sequence of plasma-cell mastitis is that of a minor inflammatory episode in the non-lactating female breast, followed later by the discovery of a lump bearing all the hall-marks of malignant disease. Some of the patients, however, give no history of prodromal inflammation and present themselves with a history and findings indistinguishable from those of cancer of the breast. Accurate diagnosis is possible only by biopsy. Even where the clinical picture is complete, guesswork is too dangerous. Frozen sections are as accurate as the pathologist who interprets them. A pathologist accustomed to this technique can differentiate between plasma-cell mastitis and malignant disease by means of frozen sections, and in the majority of cases he should be able to identify the condition by the recognition of the typical low-grade inflammatory response, characterized by periductal infiltration of plasma cells, epithelial autonomy, the appearance of giant cells, and the phagocytosis of fat. The only condition for which plasma-cell mastitis is likely to be mistaken is mammary tuberculosis, and this error can be avoided by remembering that plasma-cell mastitis involves the ducts and periductal tissues while tuberculosis has a perivascular and perilymphatic distribution. Furthermore, in tuberculosis typical tubercles are nearly always found and they may contain caseous centres. In plasma-cell mastitis the tubercles are artifactual and caseation is not discernible.

There is no evidence to suggest that plasma-cell mastitis is related in any way to malignant disease, and treatment should be conservative. Until now the majority have felt that no special treatment is indicated in the early inflammatory stage and that in the later stage, after the diagnosis has been established by biopsy, local excision of the lump is all that is required. No harm has resulted where part of the exudate has been left behind after local excision, and radical surgery is definitely contraindicated, especially in the acute stage of the disease.

In 1949, Dr. Cutler[4] reported a case—on which I commented[5]—in which very rapid regression of the mass in the breast had followed therapy by irradiation and suggested that irradiation should be tried in the acute stage with reasonable expectation that the lesion would regress and become more localized, thus facilitating surgical removal of the remnant. He also suggested the possibility that irradiation alone might suffice to resolve the lesion. In 1950, following this report, I referred a married woman of 28 years, mother of one child, with a typical plasma-cell mastitis of the left breast, confirmed by biopsy, for irradiation therapy. The condition regressed rapidly and there has been no evidence of recurrence in nearly eight years. The breast, however, is somewhat shrunken and the overlying skin is telangiectatic as a result of the irradiation.

We have, therefore, two means whereby this condition may be treated, surgery and irradiation. A third possibility is the use of steroid hormones. The causal irritant in plasma-cell mastitis is apparently a chemical one, and it seems probable that it would respond readily to the cortisone derivatives. I have not encountered a new case of plasma-cell mastitis since these hormones became available, and I would be greatly interested to hear the results in a case where they have been employed.—I am, etc.,

Ottawa, Canada. C. D. L. CROMAR.

REFERENCES

1 Cheatle, G. L., and Cutler, M., *Tumors of the Breast*, 1931, pp. 298-304. A. Arnold, London.
2 Rodman, J. S., and Ingleby, H., *Ann. Surg.*, 1939, **109**, 921.
3 Cromar, C. D. L., and Dockerty, M. B., *Proc. Mayo Clinic*, 1941, **16**, 775.
4 Cutler, M., *Brit. med. J.*, 1949, **1**, 94.
5 Cromar, C. D. L., ibid., 1949, **1**, 363.

## Moulded Handles for Disabled

SIR,—Expanded handles for knives, forks, and spoons are widely used for patients with weak grip or deformed hands suffering from such conditions as hemiplegia, multiple sclerosis, or rheumatoid arthritis. Some handles are clumsy, other devices have crevices difficult to clean. Those moulded to the individual patient's hands are to be preferred, but if professionally made by a three-stage process they are costly. Plastic wood is also used, but hardens too quickly, is apt to chip, and enamel or lacquer finish flakes off. A material was therefore sought which could be moulded by the patient gripping the handle in actual use, and which once hardened would present a clean smooth surface sterilizable by boiling and resistant to detergents and weak acids and alkalis likely to be found in food. "Vinagel" has been found to be most satisfactory for the purpose. It is made in two grades, soft (VG116) and hard (VG118), the softer being preferable. It is white, and, being of the consistency of plasticine, it can be moulded at leisure and smoothed off, retaining the main impressions of the patient's grip. The article is then heated in an oven at 150–160° C. for 20 to 30 minutes. The handle comes out a cream colour and has a slight resilience like hard rubber. Handles of table-ware made in this way have remained unchanged after several months' use in the wards with routine washing-up. Heating was done in ovens used for the sterile syringe service, but it can easily be done in a domestic oven by anyone. I am informed by the gas company that the approximate oven setting would be "C" or 2–3, but it can easily be found by trial and error. Undercooked, the handle will not be set; overcooked, it will turn brown.

I am indebted to Mr. R. Patterson, Curator, Castle Museum, York, for bringing vinagel to my notice; to Vinatex Limited, Devonshire Road, Carshalton, Surrey, for a sample supply; and to Mr. A. G. Deeks, Chief Pharmacist, City Hospital, York, for the use of sterile syringe service ovens and for testing the handles for resistance to detergents, acids, alkalis, etc.

—I am, etc.,

York. E. GORDON WILKINS.

## N-Phthalyl Glutamic Acid Imide (K 17)

SIR,—We read with interest the paper by Drs. J. McC. Murdoch and G. D. Campbell on the antithyroid activity of N-phthalyl glutamic acid imide (K 17) (*Journal*, January 11, p. 84), for we too have begun a similar investigation using a similar method. Drs. Murdoch and Campbell suggest that "it would seem unjustifiable to use the drug for long-term sedative or hypnotic therapy, pending the results of a more detailed study of its long-term effects in a larger series of patients, and notably those suffering from mild or moderately severe hyperthyroidism."

By good fortune we began with hyperthyroid patients and our results are therefore complementary to theirs. We are not yet ready to pronounce a final judgment, but our preliminary results suggest that the effects of the drug on the uptake of radioiodine in thyrotoxic patients, using single doses of 100, 300, or 400 mg., or divided doses of 300 mg. a day, for five days are negligible compared with those of carbimazole. We can confirm, as a result of experience still meagre, the sedative effects of the drug and the absence of "hangover"; but is it not a little unfair to describe as "side-effects" these actions for which the drug was introduced?—We are, etc.,

RAYMOND GREENE.
London, N.W.3. HELEN FARRAN.

## Recovery after Long-term Depressive Attack

SIR,—Dr. G. M. Woddis's article (*Journal*, December 14, 1957, p. 1412) and Dr. F. T. Thorpe's letter (*Journal*, December 28, 1957, p. 1542) show not only similarity from the psychiatric point of view of the cases described but also—as far as stated—from the physical point of view, as both patients, though over 60 at the time of their recovery, displayed no signs of arteriosclerotic changes. No more was said about their physical condition, though biochemical investigations, for example of the behaviour of the internal glands, especially the thyroid, during the period of illness and after the recovery, would be of considerable interest and could perhaps help to elucidate the cause of their disorder and/or their recovery.

The World Health Organization's recent study group on schizophrenia is reported[1] as stressing that "'psychiatric research is not a luxury,' but absolutely essential to produce advance in treatment and prevention, not only in schizophrenia but of all mental disorders." Modern treatment in psychiatry proves the dependence of the state of mind upon the balanced physiological function of the brain, which function in its turn depends on the balanced state of health of the subject. I believe that facilities must be given in future for the mental hospitals to pursue investigations at least to the same extent as done in other hospitals. The old Roman proverb "Mens sana in corpore sano" has lost nothing of its truth.—I am, etc.,

Bodmin. ERNEST E. FELDMESSER-REISS.

REFERENCE

[1] *Discovery*, 1957, **18**, 538.

## Portable Oxygen Therapy

SIR,—Dr. E. J. Moran Campbell (*Journal*, December 28, 1957, p. 1518) suggests that cyanosis on exertion be used as a measure of arterial hypoxia when deciding, in the absence of full physiological studies, which patients with respiratory insufficiency are likely to benefit from portable oxygen equipment. The unreliability of clinical assessment of cyanosis as a measurement of oxygen saturation was well demonstrated by Comroe and Botelho.[1] We suggest that a rather more reliable and yet very simple way of deciding is to make a direct comparison between air and oxygen while wearing a portable set. The ease of changing the cylinders makes such a "blind" test particularly simple to carry out.

Exercise, either walking or climbing stairs, of an intensity adjusted so that the patient is obliged to stop on account of breathlessness after two minutes breathing air, is selected. Before the assessment the patient is advised that he is only likely to get benefit from use of the equipment if he can go at least twice as far with oxygen as without. He is then shown the equipment and the type of exercise required, and is instructed to proceed until obliged to stop on account of breathlessness. It is important that the mask should be well fitting and be of the non-rebreathing type. It is also important that the patient should be adequately rested before starting exercise, and that, if he has much bronchospasm or bronchial secretion, steps should be taken to reduce these to a minimum before carrying out the test. At the end of two or more exercise periods, we tell the subject which gas the cylinders contained and discuss his performance with him.

This procedure needs only one spare detachable cylinder in addition to the portable oxygen set. In our experience this proves satisfactory both in determining which patients benefit and in satisfying those who only do so to an insignificant extent. Nevertheless, the procedure cannot be hurried and we therefore recommend that, in the event of the sets being issued under the National Health Service, this be arranged through centres where adequate assessments can be made.—We are, etc.,

Penarth, Glamorgan. J. E. COTES.
J. C. GILSON.

REFERENCE

Comroe, J. H., and Botelho, S., *Amer. J. med. Sci.*, 1947, **214**, 1.

## Action of Senna

SIR,—A 7-year-old boy was seen and found to be suffering from an acute pyrexial upper respiratory infection, with a mild pharyngitis. Because of mild constipation, the mother was advised to administer a small dose (1 teaspoonful) of "senokot," a standardized senna preparation. After the initial dose the boy helped himself to about 2 oz. (60 g.) of the granules. Some eight hours after taking the senokot he developed a red coloration of the urine, very suggestive of haematuria, and a toxic, acute nephritis was suspected, associated with his pyrexia. All physical examinations were negative and the urine did not show any abnormality other than the red colour. The patient was unaffected apart from a short period of diarrhoea, and made an uneventful recovery.

This case illustrates two facts. Firstly, that senna can produce a red coloration of the urine. According to Goodman and Gilman,[1] after the administration of senna and rhubarb, chrysophanic acid is excreted by the kidneys, and this compound colours an acid urine yellowish-brown and an alkaline urine reddish-violet. Secondly, that even in an overdose no toxic effects other than a mild diarrhoea seem to have occurred, and the patient recovered without ill effect.—I am, etc.,

Slough. DERIC B. HAWKINS.

REFERENCE

[1] Goodman, L., and Gilman, A., *The Pharmacological Basis of Therapeutics*, 1941. Macmillan, New York.

## Treatment of Chilblains

SIR,—The clinical trial of phenoxybenzamine in the treatment of chilblains reported by the South-east Scotland Faculty of the College of General Practitioners (*Journal*, December 28, 1957, p. 1521) raises the issue of the best treatment of this common winter malady. The results with phenoxybenzamine appear to be quite impressive, but the authors themselves are ready to admit that this treatment is not without its difficulties. The frequency of toxic effects does seem a distinct drawback when one considers the authors' very valid objection to the use of any toxic drug in the treatment of a benign and self-limiting condition. In addition, the profusion of drugs and remedies prescribed in the past for chilblains makes even the most statistically minded person cautious in accepting any new preparation.

The purpose of this letter is to suggest that the simplest, least expensive, and most logical approach to the treatment of chilblains should be prophylactic rather than curative. In my experience chilblains of the hands and feet, and erythrocyanosis of the legs, occur in people whose limbs are inadequately protected and are thus exposed to an unusual degree of cold. Exposure to extremes of temperature is an added or an even more important factor, for many of these patients are prone to sit close to the fire when the opportunity arises, just as they are prone to use a hot-water bottle in bed. The importance of exposure, both to heat and cold, accounts for the predominance of young females amongst patients with chilblains. Indeed, it must be a rare affliction amongst men, except amongst boys who have not yet graduated to full-length trousers. Slacks and warm socks, shoes, and gloves should be recommended, but the avoidance of overheating of the limbs is, I believe, equally important. Patients should be advised to seek a moderately heated room while indoors. They should not sit too close to an open fire, and, particularly, they should substitute extra blankets on the bed for hot-water bottles. Patients who follow this advice have, in my experience, never failed to improve quickly and in a most satisfactory way.—I am, etc.,

Dublin. RISTEARD MULCAHY.

## Amnion Implantation in Peripheral Vascular Disease

SIR,—Mr. H. Dendy Moore reported recently (*Journal*, December 7, 1957, p. 1350) on his experience with amnion implantation for peripheral vascular disease in seven cases. None of them derived any lasting benefit. Mr. E. Troensegaard-Hansen, who discovered and introduced this form of treatment (see *Journal*, August 4, 1956, p. 262), commenting on Mr. Moore's failure to confirm his own very favourable results over the past five years, suggested in a letter (*Journal*, January 4, p. 39) that Mr. Moore's poor results were due to the fact that his patients were suffering from too severe arteriosclerosis (Stage III) or that less effective commercial amnion had been used for the implants.

Mr. Troensegaard-Hansen has operated on seven of my patients during the past twelve months, with marked improvement in six cases. The single failure concerned a middle-aged diabetic suffering from severe claudication and ischaemic heart disease whose prognosis (Stage III) was poor. His claudication responded only temporarily.

Two patients had made very slow progress after a coronary infarction, but their cardiac exercise tolerance increased quickly after a single implant. Both were able to return to full-time

work and have remained well since. One of them also had a mild claudication which has now disappeared.

The fourth patient was a young girl with severe inherited erythrocyanosis crurum which had resisted several previous attempts at treatment by other means. Her legs to-day (twelve months after the implant) have a practically normal appearance and her symptoms (aching, itching, coldness) have disappeared.

Two patients, aged 62 and 65, had suffered from severe claudication for approximately two years before the implant. They are borderline Stage II/III cases in view of the severity of their claudication, although neither of them had any rest pain. Both had suffered from cold feet originally, but one later had a permanently warm left foot following a lumbar sympathectomy two years ago which, he states, had also temporarily helped him considerably with his claudication, though he had relapsed later, which led to the amnion-implant. Both had implants early in 1957 with striking benefit to their claudication. The younger patient could walk up to 20 yards (18 m.) before the implant and now walks comfortably two miles (3.2 km.). The elder man, who walked 50–60 yards (45–54 m.) on a slight up-gradient, is now able to walk several hundred yards over the same gradient. It is interesting that both patients have in the better leg a thrombosed main femoral artery from below the origin of the deep femoral artery, whilst the worse leg has a patent pulsating main femoral artery as far down as the adductor canal. This proves the great importance of a collateral blood supply.

The seventh patient also shows marked improvement up to date, both of claudication and cardiac ischaemic symptoms, since his recent operation.

My experience with Mr. Troensegaard-Hansen's method of amnion implantation leads me to believe that it holds out greater promise for effective treatment of hitherto intractable peripheral arterial disease than all previous therapeutic attempts in the past 50 years.—I am, etc.,

Sutton, Surrey. W. UNGER-HAMILTON.

## Maternal Anaesthetic Deaths

SIR,—Dr. A. H. Morley in his letter (*Journal*, December 28, 1957, p. 1543) emphasizes once again the advantages of the left lateral position in obstetric anaesthesia. While agreeing that this position has advantages when the patient regurgitates food, we must not overlook the dangers of giving an anaesthetic to a patient with a full stomach. In labour the diet should be controlled and, if necessary, the stomach emptied before a general anaesthetic is started. I would like, however, to point out that most forceps deliveries at home, and a high percentage in hospital, are outlet forceps. Most of these can easily be done under local anaesthesia. By this means the figure of 4% for home deliveries could be virtually eliminated, and the 84% substantially reduced. I strongly recommend Dr. Morley to change to local anaesthesia.—I am, etc.,

Derby. R. J. M. JAMIESON.

## Abuse of E.C.T.

SIR,—I read with interest the letter by Dr. H. Rassekh (*Journal*, December 21, 1957, p. 1493) on the abuse of electro-shock therapy. It must be admitted that in the past in many cases E.C.T. has been used to "stun" noisy patients into submission. This type of patient responds much better to humanitarian methods of handling. An example is a 64-year-old patient who had been hospitalized for 16 years. Her noisiness had caused many complaints from people living near the hospital and she had been given E.C.T. repeatedly to quieten her. In the process of implementing the open-door policy the patient was given the freedom of the hospital grounds and immediately became quiet and well-behaved. It is obvious that E.C.T. was wrongly used in this case.

I do wish to disagree with Dr. Rassekh, however, on the limitations which he puts on the indications for E.C.T. This treatment is of great value for depressives, catatonics, and in the acute manic phase. I recently treated a 60-year-old cyclothymic with arteriosclerotic heart disease and severe cardiac decompensation due to her overactivity. She did not respond to sedatives, tranquillizers, digitalis, and mercurials, and so, in spite of gross pitting oedema of the legs and ankles, she was given E.C.T. This terminated her manic phase and undoubtedly saved her life. She is now free of oedema while receiving a normal diet, without digitalis or diuretics.

A final comment is a consideration of the rarely used but valuable regressive shock therapy. In this form of treatment E.C.T. is given several times daily for ten or more days until the patient is so regressed that he is bedridden, does not know his name, is doubly incontinent, and is unable to swallow. This treatment is given to chronic paranoid schizophrenics who are completely out of contact. As the patient comes out of his regression there is a period when contact can be made and the patient is able to respond to a good psychotherapeutic atmosphere. If intensive work is done with the patients at this time an appreciable percentage will respond. In this way I have returned to the community a number of patients who would otherwise have had lobotomies performed or perhaps have remained hospitalized all their lives.

It is essential that a dynamic approach replace the old custodial psychiatry and that modern psychological methods should be adopted. It would nevertheless be a great mistake to discard valuable physical methods of treatment.—I am, etc.,

New York. M. G. JACOBY.

## Early Separation of Handicapped Children from Parents

SIR,—Mrs. B. I. Ingall, principal of a private residential deaf school, in her letter (*Journal*, December 28, 1957, p. 1545) advocates the principles of institutional accommodation of small deaf children. She states that Dr. J. E. G. Vincenzi's argument (*Journal*, November 30, p. 1304) contains many generalizations unsupported by evidence. But what sort of evidence does Mrs. Ingall herself provide, and on what basis does she make her categorical statements? For example, she says, "The late entry children are more often more maladjusted than the children who start school early." What, precisely, does she mean? What is her evidence? Can she produce statistical evidence to prove that there is a higher proportion of maladjustment among children of late entry than among children of early entry? Can she provide us with clear-cut evidence, including length of previous training, age of children, type of deafness, language attainment, etc., in each child? She says that "most cases of maladjustment arise from the child's relationship to the home, with deafness a contributory factor." Precisely how many cases can she quote? I would say that if Mrs. Ingall had provided a single short paper, giving an analysis of her cases, and so enabled us to subject it to careful scrutiny, it would have been very much more useful.

If one has to provide evidence against residential institutionalization, all one has to do is to ask some of the older children who receive this treatment and see what the answers will be. One could line up very many deaf children indeed who are or have been in residential schools from an early age. The misery and unhappiness which they frequently report are the best evidence that residential education of disabled children should be avoided as much as possible. I am saying "as much as possible" because I am fully aware that in many cases it is not possible, and for this category of children there will always be the need for residential accommodation. I think it is high time that categorical statements, unsupported by evidence, should be repudiated.—I am, etc.,

London, W.C.1 L. FISCH.

## Anti-freeze Mixtures

SIR,—I notice that your motoring correspondent, Mr. Iain Gellatly (*Journal*, January 18, p. 157), suggests that a considerable economy can be effected by general practitioners and others securing supplies of ethylene glycol from pharmacists and preparing their own anti-freeze mixture. I feel that a word of warning should be issued for those who are about to contemplate this step, since one very important factor has been overlooked in giving this advice. Not only

has ethylene glycol a greater searching action than plain water, as your correspondent correctly indicates, but it is also aggressively corrosive. For this reason all the better anti-freeze preparations placed on the market contain corrosion inhibitors, and, if properly used in a well-cleaned system, should not only protect the cooling system against damage occasioned by freezing but against corrosion of the variety of metals often encountered in the modern automobile engine. This protection will exist for the recommended life of the anti-freeze, which should be for a period of up to, but not exceeding, 12 months. In this way corrosion protection can be given to the vehicle during the summer period as well as during the winter months. For the home compounder of anti-freeze the safest and simplest inhibitor system to employ is the sodium benzoate/sodium nitrite system proposed by workers at the Chemical Research Laboratories, Department of Scientific and Industrial Research, Teddington.[1-3] The incorporation of 1% w/v sodium benzoate and 0.1% w/v sodium nitrite in the coolant will give adequate corrosion protection for a period of up to 12 months, when the coolant should be drained, the system flushed thoroughly, and fresh anti-freeze solution prepared. If it is considered preferable to remove the anti-freeze solution at the end of the winter period, replacing with plain water, a similar amount of inhibitor should be incorporated to keep the cooling system clean. The anti-freeze solution should be discarded and not reused.

During the period in which anti-freeze is in the vehicle all topping-up should be with inhibited anti-freeze solution and not with plain water, since in the majority of cases evaporation is responsible for a relatively small percentage of loss of coolant, a greater proportion being due to expansion and loss from the overflow pipe. Topping-up with water only dilutes the anti-freeze and reduces its effect. Many of your readers will perhaps feel that the complications involved are not justified by the economies made, and we would tend to agree that a good proprietary benzoate/nitrite inhibited anti-freeze is probably the safest purchase.—I am, etc.,

W. R. LUSCOMBE,
Assistant Chemical Executive,
W. J. Bush & Co. Ltd.

REFERENCES

1 Wormwell, F., and Mercer, A. D., *J. appl. Chem.*, 1952, **2**, 150.
2 —— —— ibid., 1953, **3**, 22.
3 —— —— and Ison, H. C. K., ibid., 1953, **3**, 133.

## Surfeit of Medical Papers

SIR,—I have read with interest the letter of Dr. F. O. Young (*Journal*, January 11, p. 100), in which he draws attention to the difficulties of the individual doctor in covering the present medical literature. An even more serious difficulty is occurring now, in that libraries and librarians are no longer able to ensure that all contributions on medical subjects can be kept indexed and therefore available to scientific workers. At this time only about 2,000 medical journals are covered by international indexes, out of the 6,000 published. As time goes on, this problem will become ever more serious as the present indexes are falling into arrear, and must continue to do so, unless either much more effort and money are spent on them or a smaller part of the literature is surveyed. It would seem that the time has come to make some international attack upon this difficulty.

It is obvious to any reader of medical literature that much of it is of little permanent value, although such articles as reviews are of very definite value at the time of publication. It is also evident that many articles are duplicated and even triplicated in the literature, as reports of societies, and so on. As a tentative approach to the subject, I would suggest that an international body should agree that only a limited number of medical journals be indexed, and that the editors of these journals should be quite ruthless in the acceptance of articles, only publishing those with new material. Other journals might continue to publish articles of less importance and of more ephemeral interest. This suggestion, of course, would not be a complete solution, for it depends upon human judgment, and it will overlook certain contributions which eventually will become important. None the less, it might allow a reasonable survey of the world literature to be made, thus saving a great deal of unnecessary work. It might also ensure that many important contributions are not engulfed in the morass of literature that now threatens them. The number of journals allowed to each nation, and the inclusion of journals into categories of importance, are, of course, thorny problems, but with good will the many difficulties could be overcome. I should be happy to hear the reaction of clinical and librarian colleagues to such suggestions.—I am, etc.,

Glasgow, C.2. ARCHD. L. GOODALL.

## Doctors and Human Survival

SIR,—The atomic era which is now here promises to put vast knowledge of Nature and power into our hands. But our reaction to this power is strange and in many ways inconsistent. As *The Times* on New Year's Day said, the paradox of human predicament is a deep, almost desperate, longing for peace, yoked to an instantaneous preparedness for suicidal war.

Wherever one goes it is the same; no one openly expresses a conscious desire for war, destruction, or aggression, yet, if the H bomb and its implications are raised in any conversation or meeting, people express horror: "But what can we do?" they say. And the subject is rapidly changed as though it was too painful to contemplate. When we read the papers, we find grim things happening: radioactive dust is approaching the danger level for the race, plans are going ahead for rocket bases in Scotland, the intercontinental missile is perfected, H and A bombs are carried over our heads, and disarmament conferences result in rearmament, though everyone agrees that, if the arms were used, death for both sides would result. And we are a Christian country and believe in peace and good will to all men. We even say we ought to love our enemies (though this part of Christian teaching has always been ignored). There is indeed a strange and deep inconsistency here, either a rift between the ordinary people and their leaders or else a split inside ourselves.

Now as physicians we are concerned in the survival of our patients, and as human beings we are concerned in our own survival and that of our family and of mankind. Wonderful achievements have been made by medical science during the last fifty years. The discovery of penicillin and the sulpha drugs, the conquest of syphilis and tuberculosis and malaria, the knowledge of blood chemistry and electrophysiology of the brain, and the advance of chest surgery, to mention only a few. But all these are rendered unimportant by a threat to the survival of the whole race. It is often said that as doctors we should keep out of politics; but where the destruction of all we stand for as physicians and human beings is involved we are all deeply concerned; the matter is above politics, and we must prevent the death of our patients and of our children. The time has surely come when we must make our voice heard as a profession against rearmament with nuclear weapons. We are an international profession. Medicine knows no frontiers. The doctors in all nations are our colleagues and friends. If the medical associations and colleges of all nations were but to express an opinion in favour of survival, it would have a vast effect on the minds of men and might even influence the policies of our leaders so that the dreadful vicious circle could be broken. Dare we take this step? Dare we not take it?—I am, etc.,

London, W.1. FELIX BROWN.

## Royal Hospital for Sick Children, Edinburgh

SIR,—I have been requested to collect material for a short history of the Royal Hospital for Sick Children, Edinburgh, to mark the centenary of the hospital, which will be celebrated in 1960. If any of your readers have letters, documents, or photographs relating particularly to the earlier years of the hospital which they would allow me to utilize, I should be most grateful.—I am, etc.,

Edinburgh, 4. DOUGLAS GUTHRIE.

# Obituary

## J. H. T. CHALLIS, F.F.A. R.C.S.

Dr. John Challis, senior anaesthetist to the London Hospital, died at his home at Woodford Green on January 21, aged 61.

The son of a doctor, John Humphrey Thornton Challis was born on November 8, 1896. From the City of London School he entered the London Hospital Medical College in 1913, but in the following year, being a lieutenant in the Royal Field Artillery (T.A.), he was called up at the outbreak of the first world war and served throughout as a combatant, attaining the rank of captain. When demobilized, he resumed his medical studies and qualified in 1925.

Almost at once he became interested in anaesthesia, which was to become his life's work. He was appointed resident anaesthetist at the London Hospital, and in the next few years his ability and aptitude became evident. In 1931 he was elected honorary assistant anaesthetist. His energy and application were such that, in addition to having an extensive private practice, he found time to serve as anaesthetist on the staff of many other hospitals, including the King George V at Ilford, the Southend group, the Royal National Throat, Nose and Ear, the Bearsted Memorial, the Plaistow Maternity, the Thorpe Coombe Maternity, the London Lock, and the Jubilee at Woodford. In his earlier days he pioneered the transition from "rag and bottle" to the more advanced techniques of to-day, and, in particular, introduced tracheal intubation to all his units. In 1933 John Challis was a member of a surgical team which made an epic flight to India at a time when air travel was by no means as safe as it is to-day and when the weight of equipment that could be carried was limited. A visit to America broadened still further his outlook, and, while in his own practice he favoured simple techniques perfectly executed, he would always support new methods once he had assured himself of their safety. At the Annual Meeting of the B.M.A. in 1936 he served as vice-president of the Section of Pharmacology and Therapeutics, with Anaesthetics.

The second world war saw John Challis back in uniform in 1939, this time as an anaesthetist to a mobile cerebral surgical unit. Fifteen days after its arrival in France its operation area was overrun by the Germans, and there followed three and a half years in prisoner-of-war camps, where he gave many anaesthetics in primitive and, at times, almost barbaric conditions. The privations incident to this period permanently undermined his health, and all his post-war professional activities, carried out with selfless devotion, were related to a background of gradually increasing physical debility, with never a murmur of complaint. "Dr. John," as he was always known in his home circle and to his intimates, earned universal admiration for his indomitable spirit and fortitude, and at times made us all very humble. He possessed a delightful quizzical sense of humour, and was beloved by all his colleagues, medical, nursing, and lay alike, and no less by all his patients. Perhaps the anaesthetic he liked to give above all others was for the operation of caesarean section, and in it he excelled.

Elected F.F.A. R.C.S. in 1948, John Challis was a founder member of the council of the Faculty. His contributions to medical literature were numerous. He was part author of several books, and, as president of the Anaesthetic Section of the Royal Society of Medicine in 1947–8, he reviewed the teaching of anaesthesia in his address to the Section.

His life was devoted to his work and to his family. In his younger days he was an enthusiast for winter sports, and all his life he retained his love for horses and for antique furniture. With his widow, Dr. Margaret Challis, and three daughters we mourn the passing of a true and very gallant colleague.—R. A. B.

D. V. B. writes: Others will write more adequately of the character and career of John Challis, but one who was first assistant to his department at the London Hospital would like to pay tribute to the memory of his chief. There are some details of clinical techniques which can only be taught by allowing the student to make his own mistakes, to get into deep water, and then extricating him at precisely the point of danger to the patient. Nowhere is this more true than in anaesthetics, and no other activity is as wearing to the teacher's nerves. It was a measure of his personal mastery of the technique of general anaesthesia and of the equanimity of his temperament that it was at just this type of teaching that John Challis excelled and so inspired self-confidence in his students and junior colleagues. The teaching of his specialty was close to his heart, and he made it the topic of his presidential address to the section at the Royal Society of Medicine. The eyes that twinkled above the theatre mask reflected a character that never knew malice or evoked it in others, but inspired loyalty and affection. At moments of surgical stress he was the perfect tranquillizer—devoid of toxicity. True virtuosity always appears effortless and is seldom flamboyant; such was my chief's.

## J. J. McARDLE, M.B., B.Ch.

Dr. J. J. McArdle, who was in turn teacher, soldier, and hospital medical officer, died at Belfast on January 3 at the age of 65.

John James McArdle was born at Tullynahinnera, near Castleblayney, Co. Monaghan, and received his early education at the national school in nearby Laragh and at St. Macartan's seminary. He then went on to St. Patrick's College, Maynooth, where he had a distinguished career, gaining first place in all Ireland in English, Irish, and mathematics at the first Arts examination. After leaving college he was a teacher at Roscrea for a time until he decided to study medicine. Accordingly he entered University College, Dublin, and graduated M.B., B.Ch. from the National University of Ireland in 1921, and then held the appointment of house-surgeon at St. Vincent's Hospital, Dublin. A little later he entered the Army Medical Corps and served at various places in Ireland, including Haulbowline Island, in Cork harbour, and while there was elected an honorary member of the Inter-State Postgraduate Medical Association of North America for his services to American naval personnel. He retired from the Army in 1929 with the rank of captain, and became medical officer and surgeon at Monaghan County Hospital. His services there were appreciated to the full by all who had dealings with him, for in addition to his professional skill he inspired affection and respect, and will be greatly missed in the county, particularly by his colleagues.

## H. I. MAISTER, F.R.C.S.Ed.

Mr. H. I. Maister, senior honorary orthopaedic surgeon to the Provincial Hospital, Port Elizabeth, South Africa, died at Port Elizabeth on January 4. He was 53 years of age.

Hayman Isaac Maister was born at Capetown on February 19, 1904, and studied medicine at Guy's Hospital, qualifying M.R.C.S., L.R.C.P. in 1927. After qualification he held a number of appointments at hospitals in England, including St. Olave's and St. Thomas's in London. He was elected F.R.C.S.Ed. in 1937, and specialized in orthopaedic

surgery. During the second world war he served in India with the R.A.M.C. as an orthopaedic specialist, attaining the rank of lieutenant-colonel. After the war he married and returned to South Africa, settling at Port Elizabeth, where he joined the staff of the Provincial Hospital. He is survived by his wife, also a doctor, and two children.—S. G.

## H. O. M. MEREWETHER, O.B.E., F.R.C.S.Ed.

Mr. H. O. M. Merewether, senior consulting surgeon to the hospitals in the South-East Kent Group, died suddenly at the Royal Victoria Hospital, Folkestone, on January 7. He was 54 years of age.

Henry Osborne MacCabe Merewether was born in Australia on August 31, 1903, and came of a farming family. He was educated at Geelong, Sydney University, and at Edinburgh University, where he graduated M.B., Ch.B. in 1931. After graduation he became house-surgeon to Sir David Wilkie, and, later, senior house-surgeon at the Leicester Royal Infirmary. Elected a Fellow of the Royal College of Surgeons of Edinburgh in 1936, he entered surgical partnership with Mr. H. W. L. Molesworth in Folkestone in 1937, and in the following year was appointed surgeon to the Royal Victoria Hospital. He joined the R.A.M.C. as a surgical specialist at the outbreak of the second world war in 1939, and served with distinction until 1945, having become a lieutenant-colonel in charge of a surgical division. He saw service in Eritrea, Malta, and Italy, and was appointed O.B.E. in 1945 for his services during the Italian campaign. Just after the end of the war he underwent a serious operation, but, in spite of severe physical handicap, returned to his work as a surgeon, and was actively engaged in consulting practice until a few days before his death.

M. H. K. H. writes: Henry Merewether was a good all-round surgeon, a skilled operator, and, above all, a kind and humane man. Always full of fun, he liked his patients and they liked him. He was a part of the hospital and popular with everyone, and we all miss his cheerful voice and ready wit. Almost our last memory of Henry is a happy one. He gave up his Christmas morning to carve the turkey in his ward, attired in a fantastic fancy dress. He was a particularly good speaker and raconteur. Active in his support of the Folkestone Medical Society, he was in turn its secretary, treasurer, and president, and his terms of office are remembered as outstandingly successful ones. He leaves a widow and a daughter, to whom we extend our deepest sympathy.

## J. C. BRASH, *M.C.*, M.D., F.R.C.S.Ed., D.Sc., LL.D. F.R.S.Ed.

The obituary of Professor J. C. Brash was published in the *Journal* of January 25 (p. 223).

Emeritus Professor JAMES RITCHIE writes: No formal obituary notice could convey the personal qualities which endeared Professor Brash to multitudes of students and his many friends. He had a well-organized mind stored with knowledge, apart from his professional erudition, gained from assiduous reading and his own experience; and his knowledge was at the service of any sincere inquirer. He was easy to approach, sympathetic in understanding, wise in counsel, and habitually an impish humour leavened his advice, as it did his lectures, speeches, or ordinary conversation. The photographic dossier in the anatomy department at Edinburgh, which contains a photograph of each individual who passed through his classes, is an index to his interest in his students.

Professor Brash's profound knowledge of the development of his science was illustrated in the first Haslam oration, on "Surgeon Anatomists in the History of Anatomy," which he delivered in Birmingham in 1930. His anatomical knowledge caught the public fancy in the Ruxton case, where his skilled reconstruction of dismembered bodies and alignment of a skull with a portrait contributed to the conviction of a murderer; but this was for Brash simply an exercise in anatomical detection. His research interests lay in other directions, particularly in early human embryology and in the growth and movements of teeth in the jaws of certain mammals. Following a tradition of Edinburgh anatomists he had a strong zoological bias, and his beautiful demonstrations of the growth of the teeth and bones in rats, made by feeding the animals discontinuously on madder and many other stains, was based on an accidental discovery made by John Belchier over two centuries ago. More remarkable was his demonstration that in some mammals the apparent forward movement of teeth was due to the deposition of fresh dental material at the fore edge coincident with resorption at the hind edge. Recently he had made a thorough dissection, with striking results, of the uniquely exaggerated laryngeal air-sacs of the orang-utan. His firm belief that direct personal knowledge of the structure of the body by dissection was a basic requirement for sound medical education led him to "bequeath" his body for anatomical study.

Professor Brash was much sought after as a lecturer, and he fulfilled many engagements in New Zealand, Australia, and India on a recent tour round the world with his wife. To her we would express our sympathy and to his son and daughter, who is on the staff of the Christian Medical College at Ludhiana in the Punjab.

J. K. writes: The passing of James Couper Brash is a sad event for his many friends and for the University of Edinburgh, which he served with such distinction as its professor of anatomy for twenty-three years, but his loss will be deeply felt far beyond the bounds of his native Scotland. His great reputation as a teacher and investigator, as well as the writer and editor of authoritative textbooks in his subject, had literally become world-wide. The fame of the Edinburgh school of anatomy goes back a long way in the history of medical education, and the great traditions which stemmed from the three Monros, John Goodsir, William Turner, Daniel Cunningham, and Arthur Robinson, who preceded him as occupants of the chair, were safe in the hands of James Brash. Like his predecessors, he was master of all aspects of his subject, even though in modern times anatomical science has expanded to embrace knowledge which was not even thought of a generation ago. He did more than keep abreast of advances contributed by others, however, for his alert mind and passion for investigation led him to undertake researches which established new knowledge of great practical value to the medical and dental professions of his time. One had not to work with him for long to discover his remarkable capacity for quick and accurate observation, his indefatigable industry, and his utter loyalty to truth. To watch his sound judgment and the speed with which he sifted the wheat from the chaff in appraising the theories and contentions of others was an education in itself. The amount of hard intellectual work of which he was capable in a given time was specially characteristic of him: it might be reviewing an article or a book, assessing the value of a thesis for a higher degree, or, as an examiner, reading the scripts of the candidates in an undergraduate examination—in any of these tasks his rapid and accurate penetration was the envy of colleagues who might, perhaps, match him in conscientiousness but could never keep pace with him in the race against time.

He was a great teacher, but he taught those who had the good fortune to be his students or the colleagues whom he led and inspired a great deal more than anatomy. His great humanity and kindliness never failed in word or deed, and his delightful thrusts of pawky humour would always enliven and brighten his remarks on some essential though sombre subject. The wonderful loyalty of his trust and friendship stimulated us to emulate the thoroughness and scrupulous care he brought to bear on all his work, and unconsciously and inevitably his standards became our own.

He was a keen and skilful follower of those recreations in which he found relaxation and refreshment during his well-earned holidays. *Nullum quod tetigit non ornavit,*

and he touched people graciously as well as things. A game of golf with him was a delightful experience and something to live over again in one's memory for the sheer fun of recalling the incidents he contributed to the game as such a doughty and courteous opponent. It is no wonder that to-day a countless number of colleagues and former students are remembering "Jim" Brash with pride, affection, and gratitude, and find in what they remember of his friendship and example fresh inspiration and courage to play their part more worthily in the battle of life. Their sincere sympathy goes out to the gracious lady whose devoted service and support meant so much to her husband in everything he did and undertook, and also to the son and daughter who so worthily carry on.

### C. L. PASRICHA, M.B., B.Ch.

The obituary of Lieutenant-Colonel C. L. Pasricha was published in the *Journal* of January 25 (p. 223).

M. L. A. writes: With the death of Lieutenant-Colonel C. L. Pasricha on January 11 India has lost a distinguished scientist and a sad gap has been left in the ranks of pioneers in tropical medicine. Pasricha was perhaps the youngest of that group of famous workers of the nineteen thirties—Megaw, Chopra, Napier, Acton, Knowles, Smith, and Chaudhuri, to mention a few—who consolidated the foundations of the Calcutta School of Tropical Medicine and who made some epoch-making discoveries in tropical medicine. Colonel Pasricha's interests lay mainly in the field of intestinal diseases. He was a keen observer and a voluminous writer. One can hardly pick up an issue of the *Indian Medical Gazette* of the '30s and '40s without finding one or two papers by him on bacteriophage, cholera vibrio, or epidemic dropsy. He did some very useful work on cholera and dysentery, particularly on the chemotherapy of cholera in the days when sulphonamide drugs were the fashion for every conceivable disease in the tropics. For his contributions to medical research he was awarded the Minto Medal in 1939.

Colonel Pasricha was a hard taskmaster, but an enthusiastic helper to research workers who consulted him. Most of his service was spent in Calcutta, and during the fifteen years when he was professor of pathology and bacteriology, and, later, director of the School, he gathered around him a number of young doctors and science graduates whom he trained for laboratory and field investigations into various public health problems. For these studies he used to obtain financial support from either the Indian Research Fund Association (now the Indian Council of Medical Research), or, if that failed, from industrial concerns in Bengal or Assam. How many times I have attended the annual meetings of the I.R.F.A. and seen him fight for his research assistants and the continuance of the grants for their inquiries: he used to plead their cause so well that almost invariably he carried the day. His old pupils will mourn the passing away of a valued friend and teacher.

His death is a great loss to the country, for men so well equipped and experienced and so well qualified in scientific attainments are rare. A good friend and a wise counsellor, he will be sadly missed by his friends and relations. He leaves behind two daughters, two sons, and a devoted wife who helped him in many of his activities. To the bereaved family we offer our sincere sympathy and condolence.

### T. K. MONRO, M.D., LL.D., F.R.F.P.S.

J. D. O. K writes: Perhaps one who was his eightieth house-physician may be allowed to add a personal note to the tribute paid to Professor T. K. Monro in the *Journal* of January 18 (p. 164)? In addition to his renowned library, Professor Monro had a wide range of interests varying from long country walks and fishing to a detailed knowledge of subjects as diverse as locomotive engineering and the circus. Keenly interested in music and an expert mathematician, this truly cultured man read his classics in the original. When he was 90 and almost blind, long wakeful nights had few terrors for one who could recite the plays and sonnets of Shakespeare with great feeling. Lavishly generous with his time and money, he was an ardent supporter of the Church of Scotland, the orphan homes at Bridge of Weir, the Glasgow Royal Technical College, and the Medical and Dental Defence Union of Scotland.

Professor Monro was extremely conscientious in his teaching, which lacked the sparkle of that of some of his assistants, but his lectures stood the test of re-reading in later years far better than most. He taught best by the example of his work. Quite the most remarkable bedside diagnostician one has ever been privileged to see in action, he had uncanny accuracy in prognosis. "T. K." had a delightfully delicate, dry sense of humour and would sometimes pull his associates' legs without their being aware of it. Yet he was prepared to listen to the views of the most junior member of his staff. In spite of his undemonstrative nature, his inherent kindness was quickly appreciated by his patients, and his serene equanimity helped many of them through illnesses the gravity of which they never realized when he was in charge. Perhaps the most striking features of this great doctor were his simplicity, true humility, and utter integrity. For very many years he had a vast influence for good in Scottish medicine, and a great number of Glasgow graduates will for ever treasure his memory.

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In an obituary notice of Dr. E. A. Thomson (January 25, page 224) it was erroneously stated that he married his cousin. We are informed that in fact he married the widow of a cousin.

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## Medical Notes in Parliament

### MULTIPLE PACKS

Dr. J. DICKSON MABON (Greenock, Lab.) sought, in an adjournment debate on January 23, to obtain some assurances about the provision of additional multiple packs. He made it clear that he personally disagreed with the idea of multiple packs—it put medicine into a strait-jacket, and prevented doctors from varying their treatment according to the needs of the patient. It was merely a mechanism adopted by the Government to alleviate hardship arising from the charge of 1s. per item instead of 1s. per form imposed on prescriptions in November, 1956. Since the debate on the new regulations at the time, in which the House was told that further suggestions about multiple packs would be considered, one new pack had been adopted, and that was concerned with the treatment of boils and carbuncles. It was legitimate to complain about this long delay. He asked in particular for information about multiple packs for diabetic, tuberculous, colostomy, and cardiac patients; in all these categories there was the common factor of chronic sickness which could reach a state of stabilization, so that it might be administratively possible to prescribe for long periods or for a number of commodities collectively at one time. He suggested also two possible alternative methods. It might be possible for the health departments to permit doctors to prescribe multiple packs from lists of variants, which the patient could take to the chemist. Secondly, a doctor might certify that a patient was chronically sick and would be on a certain regime of medicine and materials for two or three months, and on this certificate the Health Service executive council could issue a registration card to the patient which would make him liable only to the 1s. charge on the prescriptions regularly given by the doctor. If there was difficulty in getting the profession, through the B.M.A., to agree on a way out of the difficulty, which was understandable, the departments should suggest other solutions which might find acceptance.

### B.M.A.'s Disappointment

Mr. J. NIXON BROWNE, Under Secretary, Scottish Office, said that since the charge was introduced the health departments, with the assistance of the B.M.A., had been trying to devise further packs. The only one they had been able to devise that would seem likely to benefit a sufficient number of patients to make its production useful was a larger pack of dressings for general use.

The manufacturers were now considering production arrangements, and it was hoped that it would be in chemists' shops in 8 to 12 weeks' time. They were disappointed that it had not been found possible to devise new packs for the patients Dr. Mabon had mentioned, and the B.M.A., which had originally suggested the possibility of further packs for colostomy, diabetic, and tuberculosis patients, shared the disappointment. The main difficulty was the varied needs of different patients. Before a pack could be usefully manufactured it must be established that the standard contents would be suitable for a reasonably large number of patients. The patient would much rather have the items he needed separately prescribed than be given a standard pack which did not really meet his needs. A special dressings pack for colostomy patients had been considered, but the types of dressings required did not fall into one pattern on which a useful pack could be based. They had tried to devise for diabetics a pack containing insulin, wool, and so on, but the fundamental difficulties were that insulin had to be stored in proper conditions, and that patients had widely varying needs for different types and strengths of insulin. For tuberculosis patients the possibility of a pack containing quantities of anti-tuberculosis drugs had been examined, but again there did not seem to be a sufficiently common requirement on which to construct a pack that would be a practical proposition. So far, a pack for cardiac patients had not been considered. The Health Ministers and the B.M.A. would be only too willing to consider any suggestions for further packs.

### Double Death Duty

The Double Death Duties Bill, introduced by Mr. W. TEELING (Brighton, Pavilion, Con.) to alter the law under which the estates of couples killed as a result of the same accident may become liable to death duty twice* was given a second reading on January 24. Mr. J. E. S. SIMON, Financial Secretary to the Treasury, stated that the Chancellor of the Exchequer intended to deal with the matter in the next Finance Bill. Mr. TEELING declined the suggestion that in these circumstances he should withdraw his Bill, preferring to see how the Chancellor proposed to deal with it before reaching a decision.

### Publication of Scientific News

When Mr. R. A. BUTLER told the Commons (on January 21) that technical details of the thermonuclear research on the Zeta reactor at Harwell were to be published, Mr. R. MASON (Barnsley, Lab.) objected to this being done through the press, in driblets, and in detail in the scientific magazine *Nature*. The experiments were of such significance that there should be a statement to the House by a Minister. Mr. BUTLER disagreed. It was much better that highly scientific information should be published, as on a previous occasion, in a scientific journal. "We may then be satisfied about its accuracy, and about those who understand it publishing it. I think that is the better way," he said.

### Artificial Insemination

There were three questions on January 23 about artificial insemination. Mr. D. LLEWELLYN (Cardiff, North, Con.) asked the Prime Minister if he would recommend a Royal Commission to examine the moral, legal, and other problems arising out of the medical practice of artificial insemination. Mr. R. A. BUTLER, Home Secretary, who replied, said he appreciated the importance of this question and was considering all its aspects, but he was not yet in a position to make a statment. This answer also served for the other two, in which Mr. J. PARKER (Dagenham, Lab.) and Mr. J. GRIMOND (Orkney and Shetland, Lib.) asked for inquiry by select committee or other means to clarify the legal position.

*See *British Medical Journal*, 1957, **2**, 888.

### Radioactive Fall-out

Mrs. JOYCE BUTLER (Wood Green, Lab.) asked the Prime Minister, in view of recent evidence which she had sent him about the danger to health from radioactive fall-out, to suspend further hydrogen bomb tests. Mr. BUTLER, who replied, said "No." He was advised that the figures in the cutting sent to him were estimates made during the United States congressional hearings last July of levels of strontium-90 in human bone which might be reached in the United States if bomb tests were continued for a number of years. Even if these levels were eventually reached they would not be more than a small fraction of the level of 100 units which the reports of the Medical Research Council and of the United States Academy of Sciences regarded as the maximum permissible level for the population as a whole. Mrs. BUTLER referred to a report in the *Lancet*, which she said indicated that 10 units might be extremely dangerous from the point of view of skeletal concentration. In view of this, and of the fact that there was no threshold below which there was no genetic damage by man-made radiation, was it not imperative that the Government should seek to protect the health of the people by abandoning further tests? Mr. BUTLER told her that any extra evidence the Government obtained would be closely studied by the Medical Research Council, in conjunction with the report prepared by the United Nations' scientific committee on radiation. He could not anticipate the report, but as far as he could see the general trend of the evidence was in line with the conclusions in the M.R.C. report. Dr. EDITH SUMMERSKILL (Warrington, Lab.) pointed out that the report said that if tests continued "at the present rate"—which was before 1956—there would be a danger to the health of some now living. Since the report tests had increased. Mr. BUTLER said it was the case that there was a level of danger, but the level had not yet been reached which the M.R.C. regarded as dangerous.

Mr. R. MASON (Barnsley, Lab.) asked to what extent the M.R.C. had monitored the fall-out, to what extent they had found that radioactivity was falling along a defined global track, and what was the relative position of this country to that track. Mr. BUTLER stated that monitoring by the Atomic Energy Authority had not shown conclusively that radioactivity was falling along a defined global track, though there were indications that fall-out was somewhat heavier in the northern than in the southern hemisphere. Measurements of the fall-out in the United Kingdom and in various parts of the world were given in the report by the Atomic Energy Research Establishment, Harwell, entitled *The World-wide Deposition of Long-lived Fission Products from Nuclear Test Explosions*.

### Mental Health Report

Mr. N. DODDS (Erith and Crayford, Lab.) on January 24 asked the Minister of Health which of the main recommendations by the Royal Commission on Mental Illness and Mental Deficiency could be implemented by administrative action; and which of them would require legislation. Mr. D. WALKER-SMITH said he was advised that present powers permitted the implementation, wholly or in part, of the following recommendations: Part IV, Recommendations 6, 7, 25; Part V, Recommendations 1–4, 6, 9–11, 13–14, 15 (except the recommendation for a special capital grant); Part VI, Recommendation 9; and Part VIII, Recommendation 3. The commission's other main recommendations would require legislation.

### Plutonium Poisoning

Mr. ROY MASON (Barnsley, Lab.) asked the Minister of Health on January 27 what special arrangements had been

made for the hospitals in the southern counties to be prepared to deal with patients suffering from plutonium poisoning; to what extent research has been conducted in specialized treatment; and if all the hospitals were adequately equipped with the necessary medical supplies to deal with such an emergency.

Mr. RICHARD THOMPSON, the Parliamentary Secretary, told him that hospitals generally were equipped to deal with the toxic effects of exposure to ionizing radiations in the light of present knowledge. Research into the effects of such exposure from both internal and external sources was being actively pursued by the Medical Research Council's radiobiological research unit at Harwell and in other places in this country and abroad. He knew of no reason to make special arrangements to deal with cases of plutonium poisoning in the southern counties.

### Senior Registrars

Mr. KENNETH ROBINSON (St. Pancras, North, Lab.) wanted to know what conclusions had been reached with regard to the future of senior registrars who had completed four years' service in the grade. Mr. THOMPSON replied that the problem was to be further discussed with the Joint Consultants Committee on February 11.

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*Psychiatric Research.*—During the year 1956–7 the Medical Research Council expended £58,000 from Exchequer funds on psychiatric research, and a further sum estimated at £25,000 was spent within the National Health Service.

*Nurses.*—In the 12 months ended November 30, 1957, about 13,000 persons were admitted to the nursing profession by registration or enrolment with the General Nursing Council. The number of those who gave up nursing in that period on marriage or for other reasons was not known.

# Universities and Colleges

## UNIVERSITY OF OXFORD

In Congregation on December 14, 1957, the following degrees were conferred:

D.M.—F. J. C. Roe.

B.M.—D. I. Aitken, W. J. Harrison, M. B. Macaulay, E. H. Porter, P. G. Johnson, S. J. S. Rippon, D. R. Firth, E. S. Mucklow, P. James, J. F. Rankin, M. J. Tarsh, A. D. Lower, C. J. Lewthwaite, P. E. Moffitt, H. V. Parry, G. R. K. Wright, M. B. Bown, J. M. Wilson, M. H. Parsons, D. H. C. Surridge, J. G. R. Flint, D. O'Sullivan, Mrs. Margaret R. Matthews, Edith M. Varley, Joan D. Peacock, D. R. London (in absence).

Dr. G. S. Dawes and Professor P. R. Allison have been appointed to the Board of Governors of the United Oxford Hospitals until April 1, 1961.

The Board of the Faculty of Medicine has co-opted Surgeon Rear-Admiral James Hamilton and Dr. A. M. Cooke for a further period of two years from the first day of Hilary Term, 1958.

The Martin Wronker Prize in Medicine for 1957 has been awarded to Gordon Edward George Sladen (Merton College), and the Theodore Williams Scholarship in Pathology for 1957 to David Charles Endersby Speller, Scholar of Pembroke College.

Dr. P. B. C. Matthews has been elected to a Lectureship in Medicine at Christ Church.

## UNIVERSITY OF CAMBRIDGE

The Raymond Horton-Smith Prize for 1956–7 has been awarded to Dr. T. S. L. Beswick (*proxime accessit*, Dr. R. L. Huckstep).

In Congregation on December 14, 1957, the degree of M.D. was conferred on H. H. Stewart, P. S. Andrews, E. Sharp, and S. E. Trickey.

The following candidates have been approved at the examinations indicated:

FINAL M.B.—*Part II*: [3]J. W. Abrams, [2,3]R. A. Aiken, [2]T. H. Almond, [3]G. M. D. Archer, [1,2,3]A. M. Barnie-Adshead, [2]D. G. Beynon, [1]G. D. Blackledge, [1,3]H. P. H. Bower, [2]W. A. Brighouse, [2]J. R. Bright, [1]J. H. D. Briscoe, [1,2]M. H. Bull, [2]M. Bulmer, [1,3]H. P. R. Bury, [3]I. E. Bush, [1]A. J. Cameron, [1,2]J. R. Carling, [1]L. J. Chalstrey, [2]S. J. de Graaff-Hunter, [3]A. J. Deli, [2]R. C. Dobbie, [2]P. M. E. Drury, [2]C. Dulake, [1,2,3]P. Duré-Smith, [2]C. E. Durrant, [2]A. J. Dyer, [1,2]N. Edwards, [1]H. J. Eldridge, [2]R. H. Ellis, [2,3]R. A. Elson, [2]N. J. B. Evans, [2,3]D. S. Filer, [3]P. W. Fisher, [2]A. F. Fleming, [2]D. M. C. Forster, [1]W. E. I. Forsythe-Jauch, [2]D. Freeman, [2]E. A. French, [1,2,3]C. S. Goodwin, [2,3]N. J. C. Grant, [1,2,3]P. R. Greenfield, [1]A. Hakki, [2]N. A. Harker, [1]L. D. Heap, [2]A. H. Henderson, [2]N. E. S. Holden, [1,3]H. C. Hollingworth, [2]S. A. Janmohamed, [1,3]J. M. L. Jones, [1,2]A. W. Jowett, [2,3]B. S. Kenneth, [1,2]J. G. Lancaster, [1]Mrs. S. A. Leaver, [2]N. F. Leigh, [2,3]A. C. W. Lewis, [1,2]A. D. MacAdam, [1]N. Malcolm, [2]P. M. S. Margand, [1,3]W. H. Marshall, [1]B. S. Mather, [1,3]W. T. Menke, [1]J. Miller, [1]J. G. Miller, [2,3]A. B. J. Miller-Williams, [2]E. W. R. Oakden, [1]D. J. Parker, [1,2,3]M. Parkes, [1,3]W. P. Peeling, [1,2,3]D. J. S. Pendlebury, [3]A. D. H. Pooler, [2]N. Powers, [3]P. H. Rack, [1]R. S. O. Rees, [1]M. B. Rees-Jones, [1,3]J. B. Reynolds, [1,2,3]M. W. Riddall, [1]D. J. Riley, [1,2,3]J. Rivers-Kirby, [1,2]P. D. Rohde, [1,3]V. Rudralingam, [1]J. G. D. Simpson, [1,2,3]G. I. Sinclair, [1]D. Tidmarsh, [2]P. G. R. Tingley, [2,3]J. C. Twomey, [2]P. R. Vanstone, [3]S. O. Wamuo, [1,2,3]P. Weston, [2]G. Willett, [2]G. E. Winbolt, [2]M. C. Woodhouse, [1,2]F. C. Worlock, [1]F. G. de L. Wright. *Part I (Pathology and Pharmacology)*: A. R. Adamson, A. J. R. Anderson, E. C. Ashby, D. I. Atkinson, C. I. Backhouse, J. S. Bailey, J. E. Banatvala, M. Barry, J. R. Bartlett, P. J. F. Baskett, A. C. Bayley, P. J. Beale, D. L. Belcher, G. A. Bewley, D. A. Birkett, R. B. B. Bishton, J. Blake, S. S. Bleehen, S. A. Bolt, P. D. G. Briggs, G. C. Brill, A. Brockman, M. H. Brooke, J.-P. C. M. Brookes, E. P. Brooks, J. M. Brown, M. U. Bullen, H. P. R. Bury, W. D. Callum, I. G. Carnegie Brown, C. J. Carr, I. Chippendale, P. W. Clements, G. F. Cohen, R. D. Cohen, M. Colebrook, M. J. Corrigan, J. Craske, A. D. Crawford, P. A. Cullum, H. C. Cunningham, D. Davies, G. M. Davies, M. H. Davies, D. D. Devine, H. F. Don, A. J. Earl, J. S. Elkington, V. C. Faber, J. Farmer, G. L. Feldmar, R. C. L. Feneley, P. J. Folca, R. M. M. Fordham, P. B. Garland, T. W. Gibson, R. J. M. Gold, P. C. Green, P. H. T. Greig, J. S. Grimshaw, R. B. Harcourt, J. D. Hardcastle, D. C. Harvey, M. T. Haslam, W. R. Heaton, J. Hedley-Whyte, R. S. Hickling, N. E. S. Holden, A. A. Hooper, J. R. Hoyle, Y. P. Humphreys, I. D. Hunter-Craig, J. D. Jeremiah, M. L. Johnson, R. H. Johnson, I. N. L. Johnston, A. W. Jowett, B. S. Kennett, A. E. Kermode, R. A. Kipping, C. G. Koo, L. Kwasny, J. R. Langmaid, A. H. Y. Lee, N. K. Leiper, P. O. Liebling, R. M. Lodge, J. G. McLaggan, T. S. Matthews, W. T. Menke, R. J. Mitchell, T. M. Mitchell-Fox, T. Moreton, H. G. Morgan, M. G. E. Morgan, I. S. Muir, B. Newbigin, N. W. Oakley, M. J. O'Shea, J. D. Owen, J. S. Paddle, E. N. Payne, D. J. S. Pendlebury, A. D. H. Pooler, J. N. Powell, P. H. Rack, G. E. T. Raine, M. J. Ramsden, M. J. Raphael, M. M. R. Reid, A. Reynolds, J. C. Rice, B. Richards, D. J. Richards, G. K. Richards, M. W. Riddall, T. W. E. Robinson, N. C. Roles, H. M. Rumsey, N. Sankarayya, D. C. L. Savage, W. G. Shakespeare, J. M. Shepherd, M. R. Skelton, A. C. Smith, T. A. L. Smith, J. W. Soper, J. C. Southam, S. Spragge, J. E. Stark, J. M. Stephenson, J. D. M. Stewart, S. O. Suite, G. C. Sutton, W. J. Trowell, M. E. Tuck, H. B. Valman, M. Walker, D. M. Ward, D. B. Watkin, W. F. Whimster, D. M. Whiteford, A. Whitworth, D. H. Whyte-Venables, R. P. Wilding, M. E. Wilson, R. B. Woodd-Walker, R. Yeo.

[1]Passed in principles and practice of physic. [2]Passed in principles and practice of surgery. [3]Passed in midwifery and gynaecology.

## UNIVERSITY OF ABERDEEN

At a Graduation ceremony held on December 11, 1957, the following degrees were conferred:

M.D.—D. Emslie-Smith (with honours) and C. I. Phillips and A. J. Taylor (both with commendation). A. M. Semmence and D. Sinclair-Smith (*in absentia*).

M.B., CH.B.—Violet T. Addison, A. C. Denholm, G. R. Harvais, J. R. Miller, D. W. Rothnie.

## UNIVERSITY OF DUBLIN

### SCHOOL OF PHYSIC, TRINITY COLLEGE

The following degrees were conferred on December 11, 1957:

M.D.—A. D. H. Browne.

M.B., B.CH., B.A.O.—Mary K. Bayne, S. Bernstein, J. K. Browne, Deirdre B. Crawford, M. J. R. Dawes, J. C. M. Fitzsimon, Shirley A. Fry, J. R. Fullerton, B. Garofalides, A. Gutkowski, Joyce L. Hill, Irene F. Hurst, G. D. A. Kearney, P. P. Kelaïs, A. J. J. Kincaid, G. D. Leather, D. McClure, H. L. Morgan, J. E. E. Morgan, C. R. Pentycross, Danuta Polak, L. A. Ruben, G. J. F. Shepherd, R. D. Stevenson, K. N. Tamaklo, Margaret J. Thompson, Ann Walsh.

## UNIVERSITY OF DURHAM

In Congregation on December 14, 1957, the following degrees were conferred:

M.B., B.S.—T. N. Allison, R. Carter, I. A. Crowther, I. Deepan, E. I. Esua, W. A. Reay, Ruth H. Rishworth, Lilla Robinson, V. G. Rughani, Shirley J. Rushton.

## UNIVERSITY OF LONDON

In November, 1957, the degree of Ph.D. in the Faculty of Medicine was granted to D. McK. Moulden and Sylvia Payne.

Professor L. S. Penrose, F.R.S., has been appointed representative of the University at the tenth International Congress of Genetics to be held in Montreal from August 20 to 27, 1958.

The following have been recognized as teachers of the University in the subjects indicated in parentheses: *St. George's Hospital Medical School*, Dr. E. H. Allen (Radiology). *University College Hospital Medical School*, Lord Amulree (Medicine (Geriatrics)). *Postgraduate Medical School of London*, Dr. A. J. W. Beard and Dr. H. Woodfield-Davies (Anaesthetics); Dr. P. Hugh-Jones (Medicine); and Mr. P. G. C. Martin and Mr. A. K. Monro (Surgery). *London Hospital Medical College*, Mr. J. V. Crawford (Neurosurgery). *Institute of Cancer Research*, Dr. N. F. C. Gowring (Pathology). *St. Mary's Hospital Medical School*, Dr. R. H. Heptinstall (Pathology). *St. Thomas's Hospital Medical School*, Dr. J. D. Laycock (Anaesthetics). *Institute of Dental Surgery*, Dr. R. R. Stephens (Dental Surgery).

## UNIVERSITY OF WALES

At a Congregation held on December 21, 1957, the following degrees were conferred:

M.B., B.CH.—D. P. Birkett, Elizabeth J. Bowen, J. R. Condon, G. T. Davies, Beryl H. Evans, Elizabeth J. Evans, G. R. Ll. Evans, Audrey R. C.

Fowke, R. R. Ghose, R. J. Hilton, G. Hughes, P. A. K. Hunt, P. M. Jackson, G. D. Jones, V. Ll. Jones, D. Lewis, T. H. L. Lloyd, Mercia M. Page, R. Pash, Dhira Sonakul, Phyllis M. Thomas, L. I. Trott, R. J. Tyler, A. J. Williams.

## UNIVERSITY OF LEEDS

The following candidates have been approved at the examinations indicated:

M.D.—R. E. Rossall.
PH.D.—J. A. Sharp, M.B., Ch.B.
CH.M.—M. G. Wilson.
M.B., CH.B.—G. Hoyle (with second-class honours), T. L. Avery, Pamela M. W. Barker, J. E. Berry, I. Bower, B. Breeze-Stringfellow, J. M. Brook, Charlotte N. Capes, R. B. Dobson, F. E. Eteng, P. Foggitt, Lois F. Gendall, T. M. Hall, Joyce M. Handby, D. A. W. Hopkinson, J. L. Horner, D. A. House, H. A. Hunt, R. C. Ingrey-Senn, P. J. Knapton (with distinction in surgery), Margaret E. Lane, D. R. Liddle, M. D. McGrath, J. C. Nicholson, J. Norman, Aleksandra M. Schwetz, N. Seymour, J. M. Sinclair, P. Y. F. Taikie, Eifion Treharne, Marion E. Tyler, Sarah A. Williams.

## UNIVERSITY OF BRISTOL

The following candidates have been approved at the examinations indicated:

M.D.—A. J. Coppen, D. G. Davies, G. Walters.
PH.D.—*In the Faculty of Medicine*: Jillian M. Bond.

## ROYAL COLLEGE OF SURGEONS OF ENGLAND

At a meeting of the Council of the College held on December 12, 1957, with Sir James Paterson Ross, President, in the chair, the Begley Prize was presented to P. A. Evans, of King's College Hospital Medical School.

## ROYAL COLLEGE OF PHYSICIANS OF IRELAND

At a meeting of the College on December 6, 1957, the following candidates, who were successful in the winter final conjoint examinations, were admitted by the President, Dr. F. J. O'Donnell, to the Licence in Medicine and Midwifery:

Audrey L. Astbury, Carol G. R. Coulter, P. J. Daly, J. G. Deehan, J. A. F. Doherty, J. D. Hayes, Margaret M. Humphreys, M. Leahy, K. P. Liston, D. M. Lyndsay, J. G. McSparran, M. G. O'Donoghue, D. C. O'Neill, G. I. B. Olusanya, S. Panday, A. H. Riza, Mary P. Russell, M. A. Shaikh, O. Soyemi, R. H. M. Townend, A. de L. O'Connor.

## ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

At a meeting of the Council of the College held on November 23, the following candidates were awarded the Diploma in Obstetrics:

S. M. Ahsan, S. W. Albright, Elaine M. Allen, Sheila Allison, P. H. Amarasinghe, J. A. R. Anson, H. K. Aravi, Alison M. Armstrong, M. Ashley-Miller, P. G. Asolkar, M. J. Atwill, J. G. Banwell, A. R. Barber, C. J. Barlow, Betty Bass, A. T. Battle, W. G. Batty, J. D. C. Baxandall, Jean M. Bebell, Esther A. Bence, R. J. I. Bennett, R. J. Bennison, P. C. Bhattacharjya, R. F. Blackburn, P. W. S. Blake, S. Blumenthal, V. A. W. Blunt, May Blythe, D. G. Boddington, C. J. Booth, R. W. Bowen, J. A. Bowles, Muriel A. Boyd, A. J. Bray, M. G. Bridger, Susan M. Brocklesby, Daphne J. Broughton, Sheila N. McN. Brownlie, R. A. Burke, P. J. Burrows, W. C. Canning, Sarah Capell, G. B. Carter, R. H. Castle, R. B. Chalmers, D. P. C. Chan, J. D. Chard, June M. Cheetham, K. K. Chit, J. C. T. Church, D. B. Clark, A. D. Clift, E. C. Cockings, L. Cohen, T. L. Cooksey, D. E. Corlett, R. G. Counihan, A. Coxon, H. L. Craig, Shirley A. Craven, I. B. Crawford, J. W. Crawford, Jean E. Cree, A. D. Crew, Jill T. Crossley, M. J. Curry, A. E. Cutler, B. R. F. Daniel, H. P. Davie, J. A. H. Davies, J. G. Davies, J. M. P. Davies, B. Dawson, D. T. F. Deakin, L. S. Deane, A. R. Dewsbury, H. P. Dinwoodie, L. J. Dolan, C. J. Drouet, I. C. Dow, Sheila L. B. Duncan, Mary Ellis, D. J. Fairclough, H. P. L. Falla, T. P. Fidgeon, C. D. Fisher, M. L. Fisher, G. S. Flack, C. B. Floyd, D. E. Ford, E. R. Ford, A. J. Fry, Pamela M. Fullerton, Elizabeth George S. W. George, A. J. Gibson, Iris I. J. M. Gibson, P. M. S. Gillam, Indira Gupta, Catherine E. Hall, B. F. Hallatt, Sheila P. Hancock, T. M. Hardiker, R. G. Hardy, C. S. Harison, J. Harkness, M. B. Harris, J. F. Harrison, P. A. Harrison, G. W. Hatcher, M. J. Healy, G. W. Holmes, J. C. Hay, G. T. Haysey, R. I. Henry, G. G. Hill, M. J. Hodgson, H. M. Holden, D. Hooker, P. D. Hooper, Ann Horsburgh, Evelyn C. Hover, Rosemary Hulley, J. Hunnybun, W. Inglis, E. C. Jelly, Sarah D. Killough, D. D. Kinn, J. P. Knowles, G. B. Knox, J. R. Lamb, D. M. Lasman, Margaret R. A. Lawrence, W. J. Leishman, W. M. Lennox, D. G. Lethem, J. G. Lindsay, Yuin B. Ling, A. S. Little, Joyce F. Lloyd-Thomas, H. I. Lockett, D. Longbourne, F. J. Lowe, R. R. Macdonald, H. A. McClelland, Bertha S. McGill, Joyce A. McLeod, D. M. Mann, Stella M. Manners, I. G. Marsh, W. Marshall, R. J. Mather, J. Meecham, J. K. Millar, Alicon V. Milles, W. F. Millner, Cathie D. Moffatt, A. Moore, M. T. Morgan, Shirley P. K. Morris, B. Murphy, Aileen P. Musgrave, G. R. Myall, M. J. Mynott, J. F. MacC. Newman, Jean S. M. Ogden, C. S. Pallewela, B. K. Palmer, G. Park, Elizabeth A. M. Parkes, H. W. Parry-Williams, Joyce M. Pearce, Mavis M. Polkinghorne, W. Pollard, J. B. Pond, Ann Priestman, C. W. Pook, S. Priestman, Avril E. Reed, I. D. G. Richards, A. G. Rickenbach, Joan M. Ridley, R. P. Rosswick, Doreen Rothman, A. Roundhill, P. F. W. Rowell, R. C. I. Russell, J. F. Ryan, J. D. Salmon, E. M. Salt, D. W. I. M. Sandilands, P. R. Sathyanadhan, H. Savage, Patricia M. Scott, R. J. Scott, V. F. Shah, S. Shahani, R. K. Shelat, T. G. Skinner, R. MacC. Slater, C. C. S. Slorach, P. J. G. Smart, Alexandra G. Smith, D. I. Smith, R. G. Smith, Gillian M. W. Smith, W. T. Somerville, M. Speight, W. McA. Speirs, P. Stallabrass, T. A. M. Staunton, G. R. Stevenson, J. S. K. Stevenson, J. L. Stevenson, J. B. Stillwell, I. Stuart, J. F. Sturridge, K. M. Tankard, J. G. Teall, G. G. Temple, D. K. MacM. Thomas, T. E. Torbet, H. H. Thomson, Lucy A. Wagstaff, P. D. B. Wallice, Betty R. Warltier, Jean L. Ward, Jean M. Watkins, Betty P. Westworth, G. White, R. M. Whittington, D. Wild, J. G. P. Williams, D. B. Williamson, M. M. Win, E. M.-W. Wong, D. F. P. Wooding, J. E. Woodyard, D. Wright, D. A. Youdale.

# Vital Statistics

### England and Wales in 1957

The birth rate was the highest since 1949, and the infant mortality rate the lowest ever recorded, in England and Wales in 1957 according to provisional figures issued by the Registrar-General (Weekly Return No. 3, 1958). The number of live births registered was 722,952, giving a rate of 16.1 per thousand population as compared with 15.6 in the previous year and 16.7 in 1949. The infant mortality rate was 23.0 per thousand live births, which was 0.7 lower than in 1956. The number of deaths registered was 514,946, giving a rate of 11.5 per thousand population. This was 0.2 below the rates for 1956 and 1955 but 0.2 above the rate for 1954. The stillbirth rate at 22.4 per thousand total live and stillbirths was also the lowest annual rate yet recorded.

### England and Wales in Fourth Quarter, 1957

The birth rate in the December quarter was the highest in England and Wales since 1948. The 173,961 live births registered gave a rate of 15.4 per thousand population. The infant mortality rate of 24.8 was 1.1 above the rate for the fourth quarter of 1956. The general death rate of 13.4 per thousand population was the highest for any December quarter since 1943, when it was 14.3; in the corresponding quarters of 1956 and 1955 the rates were 11.3 and 11.1. The stillbirth rate, 22.1 per thousand live and stillbirths, was 1.1 lower than the rate in the fourth quarter of 1956.

### Week Ending January 18

The largest rises in the notifications of infectious diseases during the week ending January 18 in England and Wales were 178 for scarlet fever, from 501 to 679, and 97 for dysentery, from 574 to 671; the largest falls were 453 for measles, from 2,888 to 2,435, 233 for acute pneumonia, from 1,292 to 1,059, and 18 for whooping-cough, from 460 to 442.

The largest declines in the incidence of measles were 112 in Glamorganshire, from 417 to 305 (Swansea C.B. 199); 64 in Hertfordshire, from 127 to 63; 62 in Derbyshire, from 131 to 69. The number of notifications of scarlet fever rose slightly in most areas in the country; the largest rise was 53 in Lancashire, from 45 to 98, due to sporadic cases throughout the county. Only small changes were reported in the local trends of whooping-cough. 2 cases of diphtheria were notified, being 5 fewer than in the preceding week. A fall in the number of notifications of acute pneumonia was recorded in most regions, but in the north-midland counties the notifications rose from 64 to 87, and in the northern counties from 75 to 101.

4 of the 7 cases of paratyphoid fever were notified in Buckinghamshire, Buckingham R.D. Both cases of typhoid fever were notified in Northumberland, Alnwick R.D.

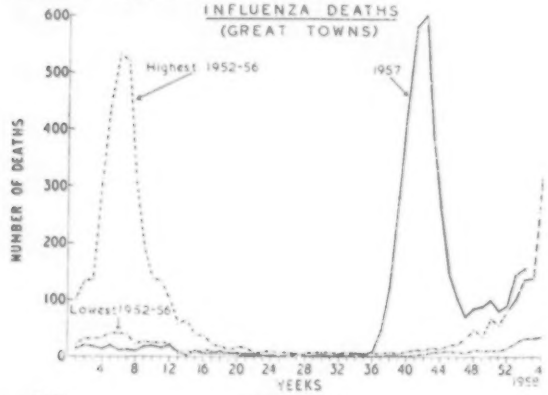
The notifications of acute poliomyelitis numbered 31, and these cases were 6 fewer for paralytic and 1 more for non-paralytic cases than in the preceding week. The largest returns were Buckinghamshire 4 (Wolverton U.D. 2) and Derbyshire 4 (Chesterfield R.D. 2).

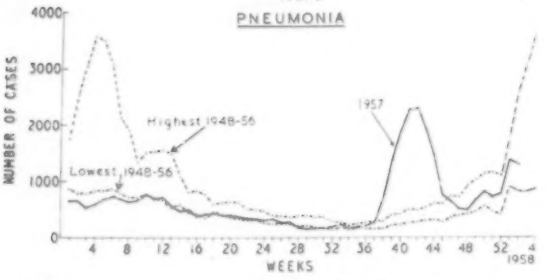
The largest increases in the number of notifications of dysentery were 37 in Lancashire, 35 in Yorkshire North Riding, and 31 in Middlesex. The largest centres of infection during the week were Lancashire 206 (Oldham C.B. 79, Manchester C.B. 33, Liverpool C.B. 23, Eccles M.B. 13, Royton U.D. 10), London 135 (Hammersmith 35, Islington 22, Holborn 21, Chelsea 15), Yorkshire West Riding 80 (Sheffield C.B. 39), Middlesex 44 (Willesden M.B. 21), Yorkshire North Riding 37 (Easingwold R.D. 34), Durham 33, and Northumberland 22 (Newcastle upon Tyne C.B. 12).

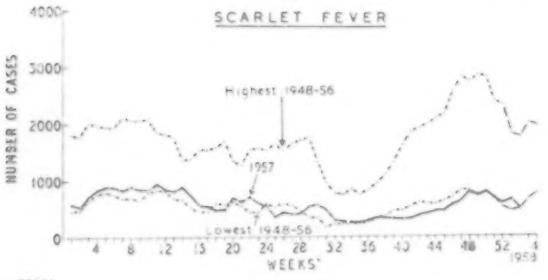
The largest outbreak of food-poisoning during the week was 41 cases in Yorkshire East Riding, Haltemprice U.D.

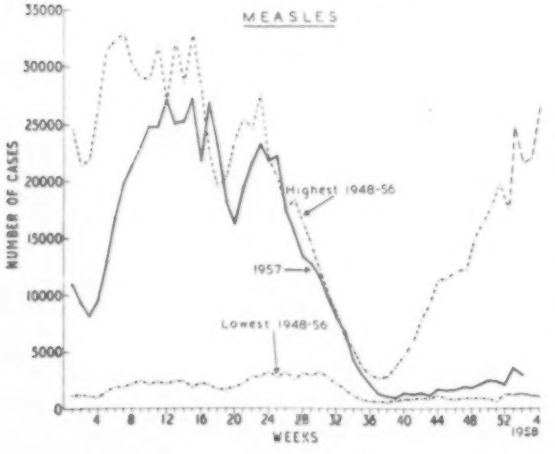
### Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases (deaths for influenza) of certain diseases notified weekly in England and Wales (great towns for influenza). Highest and lowest figures reported in each week during the years 1948–56 (influenza, 1952–6) are shown thus - - - - - -, the figures for 1957–8 thus ————. Except for the curves showing notifications in 1957–8, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.




## INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **January 11** (No. 2) and corresponding week 1957.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

| CASES in Countries and London | 1958 Eng. & Wales | 1958 Lond. | 1958 Scot. | 1958 N. Ire. | 1958 Eire | 1957 Eng. & Wales | 1957 Lond. | 1957 Scot. | 1957 N. Ire. | 1957 Eire |
|---|---|---|---|---|---|---|---|---|---|---|
| Diphtheria .. | 7 | 1 | 6 | 0 | 4 | 9 | 2 | 6 | 0 | 2 |
| Dysentery .. .. | 574 | 119 | 114 | 7 | 4 | 530 | 49 | 183 | 2 | |
| Encephalitis, acute | 3 | 0 | | 0 | | 3 | 0 | | 1 | |
| Enteric fever: Typhoid .. | 2 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 1 |
| Paratyphoid .. | 7 | 0 | 1 (B) | 0 | | 4 | 1 | 1 (B) | 0 | |
| Food-poisoning .. | 139 | 14 | 26 | 0 | | 162 | 29 | 22 | 0 | |
| Infective enteritis or diarrhoea under 2 years .. .. | | | | 11 | 11 | | | | 12 | 13 |
| Measles * .. .. | 2,888 | 39 | 90 | 83 | 13 | 9,281 | 674 | 617 | 321 | 119 |
| Meningococcal infection .. .. | 34 | 3 | 15 | 0 | | 35 | 3 | 7 | 0 | 3 |
| Ophthalmia neonatorum .. .. | 22 | 1 | 12 | 0 | | 25 | 3 | 9 | 0 | |
| Pneumonia † .. | 1,292 | 123 | 568 | 6 | 21 | 648 | 39 | 417 | 11 | |
| Poliomyelitis, acute: Paralytic .. | 28 | 1 | 2 | 0 | 6 | 47 | 7 | 2 | 0 | 17 |
| Non-paralytic .. | 8 | 0 | | | | 25 | 3 | | | |
| Puerperal fever § .. | 235 | 64 | 22 | 1 | | 224 | 32 | 5 | 1 | |
| Scarlet fever .. | 501 | 34 | 69 | 12 | 6 | 528 | 33 | 84 | 13 | 19 |
| Tuberculosis: Respiratory .. | 566 | 68 | 82 | 30 | | 543 | 57 | 124 | 16 | |
| Non-respiratory | 50 | 6 | 8 | 8 | | 84 | 6 | 7 | 1 | |
| Whooping-cough .. | 460 | 17 | 38 | 4 | 6 | 2,486 | 122 | 507 | 15 | 24 |

| DEATHS in Great Towns | 1958 Eng. & Wales | 1958 Lond. | 1958 Scot. | 1958 N. Ire. | 1958 Eire | 1957 Eng. & Wales | 1957 Lond. | 1957 Scot. | 1957 N. Ire. | 1957 Eire |
|---|---|---|---|---|---|---|---|---|---|---|
| Diphtheria .. | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Dysentery .. .. | 1 | 0 | | 0 | | 0 | 0 | | 0 | |
| Encephalitis, acute | | 0 | | | | | 0 | | | 0 |
| Enteric fever .. | 0 | 0 | 0 | 0 | | 0 | 0 | 0 | 0 | |
| Infective enteritis or diarrhoea under 2 years .. .. | 11 | 0 | 0 | 0 | 1 | 6 | 0 | 3 | 0 | 1 |
| Influenza .. .. | 155 | 21 | 2 | 0 | 4 | 21 | 0 | 0 | 0 | 0 |
| Measles .. .. | | 0 | 0 | 0 | 0 | | 0 | 0 | 0 | 0 |
| Meningococcal infection .. .. | | 1 | 0 | | | | 1 | 1 | | |
| Pneumonia .. | 678 | 117 | 61 | 12 | 11 | 348 | 39 | 28 | 17 | 12 |
| Poliomyelitis, acute | 7 | 1 | | 0 | 0 | 5 | 1 | | | 0 |
| Scarlet fever .. | | 0 | 0 | 0 | 0 | | 0 | 0 | 0 | 0 |
| Tuberculosis: Respiratory .. | 77 | 10 | 9 | 1 | 3 | 76 | 11 | 9 | 2 | 2 |
| Non-respiratory | | 2 | 1 | 0 | 0 | | 0 | 0 | 0 | 0 |
| Whooping-cough .. | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 |
| Deaths 0–1 year .. | 270 | 43 | 58 | 8 | 11 | 217 | 29 | 35 | 12 | 17 |
| Deaths (excluding stillbirths) .. | 8,129 | 1254 | 839 | 134 | 202 | 6,023 | 851 | 617 | 142 | 177 |
| **LIVE BIRTHS** .. | 8,700 | 1313 | 1142 | 238 | 353 | 8,525 | 1269 | 1118 | 252 | 410 |
| **STILLBIRTHS** .. | 219 | 26 | 28 | | | 205 | 31 | 18 | | |

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

# Medical News

**Chair of Materia Medica, Edinburgh.**—Dr. W. L. M. PERRY has been appointed to the Chair of Materia Medica at Edinburgh University. Professor J. H. GADDUM, F.R.S., whom Dr. Perry will succeed on September 30, is leaving Edinburgh to become director of the Agricultural Research Council's Institute of Animal Physiology at Cambridge (see *Journal*, November 2, 1957, p. 1062). Dr. Perry, who is 36, is director of the department of biological standards at the National Institute for Medical Research. He graduated M.B., Ch.B. at St. Andrews University in 1943, proceeding M.D. in 1948. His main publications have been on the pharmacology of the autonomic nervous system, though he has also written on the technical aspects of drug standardization. Latterly Dr. Perry has been concerned with the safety- and potency-testing of the poliomyelitis vaccine used in Britain. His successor as director of the department of biological standards at the National Institute will be Dr. D. G. EVANS.

**Retirement of Sir Stanley Davidson.**—The court of Edinburgh University announces that Sir STANLEY DAVIDSON is retiring from the chair of medicine at the end of March. He will have held the chair for 20 years. Sir Stanley will be 64 next month.

**Bloomsbury Coffee Pot.**—On January 28 the Bloomsbury Coffee Pot was inaugurated. This is the third of these clubs to be opened in London. Their purpose is to give university graduates and young professional people the chance to meet each other in congenial surroundings: they aim, in fact, to fill one of the gaps caused by the present-day decline of private entertaining. Membership of the Bloomsbury Coffee Pot will be restricted to between 300 and 400 persons, aged 19–30, with the sexes in more or less equal numbers. The annual subscription is about £2. The club will meet weekly on Tuesday evenings at the Y.W.C.A. Central Club, Great Russell Street, London, W.C.1. There is also a club in London on the same lines—the "57 Society"—for those over 30; and there are several Coffee Pot clubs in the provinces. Further information about these clubs may be obtained from the secretary, National Coffee Pot Committee, 108, Baker Street, London, W.1.

**New Journals.**—Four new journals have recently come to our notice. *Perspectives in Biology and Medicine* is a quarterly sponsored by the Division of Biological Sciences of Chicago University. It is to be orientated "toward man and his illnesses, but with appreciation of the fact that the roots of medical theory reach into all fields of biology," and will contain "original essays" (new hypotheses, interpretative essays, and autobiographical sketches), leaders, letters, and book reviews. The editors are Dr. D. J. INGLE (Chicago) and Dr. S. O. WAIFE (Indianapolis). The advisory board includes the names of Sir HENRY DALE, O.M., and Dr. G. E. W. WOLSTENHOLME. The publishers are the University of Chicago Press, but the Cambridge University Press, 200, Euston Road, London, N.W.1, are acting as agents in Britain (U.S.A. subscription rate, $6 annually). J. B. Lippincott Company, of Philadelphia, have launched *Diseases of the Colon and Rectum*, which aims to provide authoritative information on medical and surgical advances in this field. The journal will be international in character and cover basic research in metabolism, pathology, virology, and radiology, as well as clinical practice; abstracts of the world literature will also be included. The editor-in-chief is Dr. LOUIS A. BUIE, sen. (Rochester), and the advisory board includes Mr. A. LAWRENCE ABEL, Dr. CUTHBERT DUKES, and Mr. W. B. GABRIEL. The agents in Britain are the Pitman Medical Publishing Company, 45, New Oxford Street, London, W.C.1, and the annual subscription, including postage, is £5. The *American Journal of Cardiology*, which will appear monthly, is stated to be the official journal of the American College of Cardiology. The editor-in-chief is Dr. SIMON DACK, of New York, and among the editorial consultants is Dr. PAUL WOOD. This journal aims to be "a teaching journal, dedicated to practising clinicians and cardiologists." The foreign annual subscription rate is $15, and the publishers are the American Journal of Cardiology, Inc., 11, East 36th Street, New York, 16. *Journal of Ultrastructure Research* is edited by Drs. F. S. SJÖSTRAND and A. ENGSTROM, both of the Karolinska Institute, Stockholm, and is published by the Academic Press Inc., 111, Fifth Avenue, New York, 3. It is a quarterly and the annual subscription is $15. The first issue contains seven original articles of which two are in French. Among the editorial board are Dr. V. E. COSSLETT, Dr. H. E. HUXLEY, and Professor J. T. RANDALL, F.R.S.

**M.R.C.O.G.**—At a meeting of the council of the Royal College of Obstetricians and Gynaecologists on January 25 the following were elected members:

V. Balachandran, B. Banerji, S. K. Basu, F. X. Bencini, O. Bolitho, R. T. Booth, C. A. Braga, A. F. Bushby, A. S. F. Butcher, D. P. Das, F. J. De Maria, R. E. ff. Devitt, P. H. Drake, I. M. Duthie, M. G. Eldridge, D. V. I. Fairweather, F. G. Feinstein, N. K. Ghose, P. R. G. Gordon, H. M. Gough, J. L. Hanington, G. H. Harris, J. C. Hartgill, C. H. Hodge, H. E. Hughes, T. R. Hunt, A. H. John, S. Khanna, H. Kramer, D. K. C. Kwan, D. J. Mackay, P. C. Mackay, S. A. Martyn, G. G. Matthews, R. J. Mitchell, A. K. Mukherjee, J. M. North, J. North, O. K. Ogan, W. H. Patterson, P. A. Rachow, K. Sankari, B. Shieff, M. K. Si, M. L. Smith, I. H. F. Swain, M. A. T. Tolley, R. D. Upton, B. C. Uys, A. J. Van Amerongen, J. A. Verzin, D. W. Warrell, J. Willocks.

**Royal Microscopical Society.**—Mr. JOHN BUNYAN, L.D.S. R.C.S., of St. Mary's Hospital Medical School, Paddington, was elected president at the society's recent annual meeting. He is the society's fiftieth president. The society was founded in 1839 and granted a Royal Charter in 1866.

**North of England Obstetrical and Gynaecological Society.**—The society's annual meeting was held in Manchester on January 17. The following officers were elected for 1958: *President*, Dr. E. A. Gerrard; *vice-presidents*, Miss M. Evans (Manchester), Mr. C. J. K. Hamilton (Liverpool), Mr. G. W. Theobald (Leeds), Professor C. S. Russell (Sheffield), and Mr. F. J. Burke (Newcastle); *hon. treasurer*, Mr. C. H. Walsh; *hon. general secretary*, Miss E. Mills; and *hon. reporting secretary*, Miss U. M. Lister.

**Dr. P. J. Delaney.**—The retirement of Dr. P. J. DELANEY from the medical secretaryship of the Irish Medical Association will be noted with regret by his many friends in Britain. He did much to foster good will between members of the medical profession in the two countries.

## COMING EVENTS

**Liverpool University Medical Students' Society.**—The annual dinner for past and present members of the society will be held at the Mecca, Sefton House, Liverpool, on February 6. Tickets (25s.) may be obtained from the medical dinner secretary, Medical School, University, Liverpool, 3.

**Contraceptive Technique.**—MRS. MARIE STOPES, D.Sc., will give a lecture-demonstration on contraception at the Mothers' Clinic, 108, Whitfield Street, London, W.1, on February 6, at 2.30 p.m. No fee, but tickets should be obtained in advance.

**Royal Medico-Psychological Association.**—Course of lectures at the Royal Society of Medicine, February 10 and 11. Further particulars and tickets from the association at 11, Chandos Street, London, W.1.

**International Diabetes Federation.**—Third Congress of the International Diabetes Federation, Düsseldorf, July 21–25, 1958. Details from the congress office, II Medizinische Klinik der Medizinischen Akademie, 5, Moorenstrasse, Düsseldorf.

**International Congress of Physiological Sciences.**—The 21st congress (physiology and pharmacology) will be held in Buenos Aires, August 9–15, 1959, under the presidency of Professor BERNARDO A. HOUSSAY. Further details from the congress secretary, Buenos Aires, Argentina.

**International Congress of Photofluorography.**—Third international congress, August 20–23, in Stockholm; organized by the International Society of Photofluorography in conjunction with the International Union against Tuberculosis. Details from the congress secretariat, Post-box 5097, Stockholm, 5.

**Sixth International Congresses on Tropical Medicine and Malaria.**—September 5–13, 1958, in Lisbon. Details from the secretary-general, Instituto de Medicina-Tropical, Lisbon, Portugal.

**International Society of Hematology.**—Seventh congress, September 7–13, in Rome. Preliminary programme: immunohaematology, haemorrhagic disorders, leukaemia, anaemia, "nucleonics," the spleen and R.E. system. Details from the secretary's office, Istituto di Patologia Medica, Policlinico Umberto I, Rome.

## NEW ISSUES

### SPECIALIST JOURNALS AND ABSTRACTS

*All the journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.*

**British Journal of Ophthalmology.**—Issued monthly (£6 annually). The new issue, Vol. 42, No. 1, includes:

VASO-MOTOR FACTOR IN GLAUCOMA. E. Gordon Mackie.
THE POSTERIOR DEGENERATIVE LESION OF ONCHOCERCIASIS. F. C. Rodger.
A CHANGEABILITY TEST OF AQUEOUS OUTFLOW RESISTANCE. E. Linnér.
BURIED ORBITAL IMPLANT WITH EXTRA-CONJUNCTIVAL EXTENSION. Stanislaw Gebertt.

**Abstracts of World Medicine.**—Issued in the first week of each month, this journal contains abstracts of important papers selected from the current medical literature of the world. Annual subscription £4 4s.

## SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

### Saturday, February 1

KENT PAEDIATRIC AND CHILD HEALTH SOCIETY.—At Children's Department, Farnborough Hospital, 3 p.m., Symposium on the Comprehensive School. Speakers, Miss M. Miles, Miss O. A. Laker, Mr. S. E. Willineham, and Mr. R. T. Sumner.

### Monday, February 3

GUY'S HOSPITAL.—5 p.m., Endocrine Demonstration. Hypoparathyroidism and Pseudo-Hypoparathyroidism. Guest speaker, Dr. R. R. de Mowbray.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. B. G. O. Ackner: Emotions and the Cardiovascular System.

### Tuesday, February 4

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. M. G. P. Stoker: Growth of Viruses.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. C. D. Calnan: Haemangiomata.
INSTITUTE OF NEUROLOGY.—5.30 p.m., Dr. A. SUBIRANA (Barcelona): Prognosis of Aphasia.
ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Milroy Lecture by Dr. Cicely D. Williams: Social Medicine in Developing Countries.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute Theatre, 5 p.m., Mr. J. D. S. Flew: Induction of Labour.
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Mr. G. C. Knight: Spinal Cord Lesions.

### Wednesday, February 5

ASSURANCE MEDICAL SOCIETY.—At Medical Society of London, 5 p.m., Dr. J. L. Livingstone: Asthma and Bronchitis in Relation to Life Assurance.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. W. Riddell: Actiology of Fungous Infections.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. Paul Wood: Current Problems Relating to Congenital Heart Disease.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Dr. I. Friedmann, Dr. D. A. Osborn, and Dr. S. S. Epstein: clinico-pathological conference.
INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. A. W. Badenoch: Haematuria.
MANCHESTER MEDICAL SOCIETY: SECTION OF MEDICINE.—At Large Anatomy Theatre, Manchester University, 4.30 p.m., Presidential Address by Professor W. Schlapp: Charles Scott Sherrington—A Centenary.
MIDLAND MEDICAL SOCIETY.—At Birmingham Medical Institute, 8.15 p.m., Dr. Dorothy Campbell: Medical Treatment of Glaucoma.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., lecture by Dr. A. E. Mourant.

### Thursday, February 6

BEDFORD COLLEGE.—5.15 p.m., public lecture by Professor J. Z. Young, F.R.S.: The Human Brain—The Brain and its Connexions (illustrated).
BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. C. S. Hallpike, F.R.S.: Remarks upon the Scientific Basis of Otological Practice.
FACULTY OF HOMOEOPATHY.—5 p.m., Dr. Alva Benjamin: Medical Profession's Responsibility for the Health of the Community.
LIVERPOOL MEDICAL INSTITUTION.—8 p.m., Dr. T. Black: Marcello Malpighi and His Influence on Our Knowledge of the Spleen.
LONDON UNIVERSITY.—At Middlesex Hospital Medical School, 5 p.m., special university lecture in human anatomy and morphology by Professor T. S. Westoll, F.R.S.: Pattern and Form in the Vertebrate Skull—A Study in Plastic Deformation and its Limits.
ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Milroy Lecture by Dr. Cicely D. Williams: Social Medicine in Developing Countries.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. M. A. Partridge: postgraduate demonstration in psychiatry.
SCIENTIFIC FILM ASSOCIATION.—At Royal Photographic Society, 7 p.m., Dr. E. J. G. Beeson: Discharge Lamps: Principles and Practice.
WEST OF ENGLAND CHILD HEALTH GROUP.—At Department of Child Health, Bristol Royal Hospital for Sick Children, 8.30 p.m., Miss J. M. Hood, M.A.: West Indian Families.

### Friday, February 7

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. P. J. Hare: clinical demonstration.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. F. H. Scadding: clinical demonstration.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., clinical discussion for general practitioners by Dr. N. G. Hulbert: Functional Factors in Ear, Nose, and Throat Diseases.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 10 a.m., Sir Cecil Wakeley, Bt., K.B.E.: Surgery of the Breast. (2) 4 p.m., Dr. I. McD. G. Stewart: Some Changing Ideas About Hypertension.
ROYAL MEDICAL SOCIETY, EDINBURGH.—8 p.m., Sir Walter Mercer, P.R.C.S.E.: Russian Surgery and Other Things.
ROYAL MEDICO-CHIRURGICAL SOCIETY OF GLASGOW.—At Royal Faculty of Physicians and Surgeons of Glasgow, 8.30 p.m., Dr. Alex. Brown, Dr. Hugh Conway, and Dr. Ian Wang: Treatment of Leukaemia.
WHIPPS CROSS HOSPITAL MEDICAL SOCIETY.—8.30 p.m., Dr. H. W. Balme: Rest and Exercise.

## BIRTHS, MARRIAGES, AND DEATHS

### BIRTHS

**Davies.**—On January 8, 1958, at Morriston Hospital, Swansea, to Marie, wife of Dr. D. M. Davies, a sister for Sian, John, and Sheila—Fiona Mari.

**Smith.**—On January 23, 1958, at Cardiff Maternity Hospital, to Helen (formerly Reid), R.G.N., wife of William G. Smith, M.D., M.R.C.P.Ed., a daughter—Heather Jane.

**Winkler.**—On January 21, 1958, at the Westminster Hospital, London, S.W., to Fay, wife of Dr. John Winkler, a sister for Philippa and Elisabeth.

### DEATHS

**Burnet.**—On January 8, 1958, at 14, Cumin Place, Edinburgh, James Burnet, M.D., F.R.C.P.Ed., LL.B.

**Caffry.**—On January 16, 1958, in a nursing-home, Charles Robert Caffry, M.R.C.S., L.R.C.P., of 124, Cherry Hinton Road, Cambridge, aged 71.

**Drummond.**—On January 18, 1958, in Glasgow, Graham Thomson Drummond, M.B., Ch.B., formerly of Coatbridge, Lanarkshire.

**Duff.**—On January 14, 1958, at 276, Wilbraham Road, Manchester, John Duff, M.B., Ch.B.

**Edwards.**—On January 17, 1958, at 5, Brunswick Street, Huddersfield, Yorks, Thomas Henry Edwards, F.R.C.S., aged 81.

**Egan.**—On January 16, 1958, at Westminster Hospital, London, S.W., Kieran Egan, M.B., B.Ch., of 1, Almond Avenue, Ickenham, Middlesex, formerly of Ruislip, Middlesex.

**Gaff.**—On January 10, 1958, at the home of his nephew, Woodstock, Chinthurst Lane, Shalford, Guildford, Surrey, James Gaff, M.B., late of Hammersmith, London, W., and Abinger Common, Surrey, aged 82.

**Greatorex.**—On January 14, 1958, at Lower Hall, Barkisland, Halifax, Yorks, Robert Wilkinson Greatorex, M.B., Ch.B., aged 71.

**Hamilton.**—On January 13, 1958, at Herne Bay, Kent, Frederick Wood Hamilton, M.D., M.R.C.P., D.P.H.

**Harding.**—On January 8, 1958, Geoffrey Duncan Harding, M.B., Ch.B., Colonel, late R.A.M.C., retired, of Green Shutters, Velmead Road, Fleet, Hants.

**Isserlis.**—On January 9, 1958, at Cheriton Fitzpaine, Crediton, Devon, Karl Peter Isserlis, M.R.C.S., L.R.C.P., aged 45.

**Loosely.**—On January 18, 1958, at Bryn Derwen, Hindhead, Surrey, Charles James Loosely, M.R.C.S., L.R.C.P., aged 87.

**Macarthur.**—On January 16, 1958, at the Royal Infirmary, Glasgow, George Archibald Macarthur, M.B., Ch.B., of Firgrove, Oban, Argyll.

**Merewether.**—On January 7, 1958, at the Royal Victoria Hospital, Folkestone, Kent, Henry Osborne MacCabe Merewether, O.B.E., M.B., F.R.C.S.Ed., of Lympne Hall, Lympne, Kent.

**Obermer.**—On January 12, 1958, Edgar Obermer, M.D., of Les Hautes Roches, Cinais, Indre et Loire, France.

**Sayers.**—On January 16, 1958, at Gosfield Hall, near Halstead, Essex, Bernard Edward Patrick Sayers, M.R.C.S., L.R.C.P., Surgeon Lieutenant-Commander, R.N., retired, late of Welwyn Garden City, Herts, aged 69.

**Stoneham.**—On January 14, 1958, at the Canadian Memorial Hospital, Cliveden, Bucks, Frederick James Russell Stoneham, M.R.C.S., L.R.C.P., F.F.A. R.C.S., of Merryacre, Cherry Tree Road, Farnham Royal, Bucks, aged 48.

**Todd.**—On January 11, 1958, at Rose Cottage, Cuckfield, Sussex, Harry Campbell Todd, M.B., F.R.C.S.Ed.

**Wilkinson.**—On January 9, 1958, at 4, The Avenue, Starbeck, Harrogate, Yorks, Sydney Carter Wilkinson, M.B., Ch.B.

# Any Questions?

*We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.*

### Intravenous Fructose Therapy

**Q.**—*During severe metabolic stress, intravenous fructose is said to be more efficient than intravenous glucose. The reason given is that fructose is metabolized more directly than glucose, and via a path independent of insulin. If this is so, why is glucose chosen in preference to fructose as the standard sugar for intravenous use?*

**A.**—Fructose (laevulose) metabolism may follow a number of pathways that are independent of the action of insulin, and in a diabetic patient the fructose tolerance curve is similar to that of a normal subject. Unfortunately, however, very little fructose is taken up or utilized by tissues such as the muscles or brain. Fructose metabolism is largely confined to the liver, and here it is more rapid than that of glucose; this probably explains why the protein-sparing action of fructose is greater than that of glucose. This limited advantage must be offset against the much greater cost of fructose and the tendency of many fructose preparations to cause reactions when given intravenously. In the treatment of severe diabetic ketosis fructose has proved disappointing because much of it is converted to glucose, insulin requirements are increased, and interpretation of blood-sugar levels is complicated by the fact that if done by the usual methods they give a combined figure for glucose plus fructose. The possible clinical applications of fructose therapy have been reviewed by Renold and Thorn,[1] though its possible disadvantages were not emphasized sufficiently.

REFERENCE

[1] Renold, A. E., and Thorn, G. W., *Amer. J. Med.*, 1955, **19**, 163.

### Fumes from Paraffin Stoves

**Q.**—*What gases and fumes are generated by paraffin stoves? Under ordinary conditions of ventilation do they constitute any health hazard?*

**A.**—When paraffin (kerosene) is burned completely the products are carbon dioxide and water vapour. In addition traces of oxides of nitrogen may be evolved, as is the case when any fuel is burnt at high temperatures. Smoke and kerosene vapour result if the stove is very badly adjusted. Incomplete combustion of any fuel can lead to the production of carbon monoxide, but paraffin heaters are designed to ensure that, given an adequate supply of air, combustion is complete. Reputable appliances conform to the very strict requirements of British Standard Specification 2049, Pt. 1, 1953, one clause of which states that "the completeness of combustion shall be such that the ratio $CO/CO_2$ never exceeds 0.02 at any rate of burning between the minimum operational rate and the rate obtained at the maker's recommended full flame size." It is noted that in ordinarily well-made appliances the ratio is 0.005 or less for normal rates of burning.

There is no evidence to suggest that the heaters, when used according to the maker's clear instructions in rooms with reasonable ventilation, constitute any hazard to health.

### Vitamins for the Elderly

**Q.**—*Is there any reliable evidence that vitamins benefit (1) loss of hearing, (2) loss of memory, (3) loss of hair in elderly people?*

**A.**—The volume of research on vitamins is so intense that lesser-known sources of information may be overlooked, but there is no well-known and accepted evidence to show that they are of any benefit in these conditions. On the other hand, old people are often malnourished, and it would be rash to conclude that improvement of their diet, including the provision of vitamins, might not sometimes improve hearing and memory. Nutritional factors appear to play only a minor role, if any, in the causation of baldness.

### Road-layers and "Tar"

**Q.**—*What industrial hazard do asphalt, tar, etc., constitute for road-layers? What is "pitchmastic" and why is it regarded as a particular hazard for those with chest complaints?*

**A.**—Road-layers handle a variety of materials popularly referred to as "tar." These comprise asphalt, bitumen, pitch, and tar. Spreading of these materials is frequently done hot at temperatures around 300° F. (148.8° C.). Dense irritant fumes are evolved, but many people like their aromatic odour. Indeed these fumes have long been esteemed as efficacious in the treatment of whooping-cough. Bitumen may be taken as representative of the group. It is the basic material of the road aggregate, comprising 8 to 15%. It is a mixture of complex hydrocarbons, and the volatile products which are inhaled include benzene, toluene, and naphtha. The mineral part of the mass is composed of crushed limestone and igneous rocks. Heavy oils are used as a flux, and these contain appreciable amounts of sulphur, which on heating is released as sulphurous gases. Road-layers are exposed to contact with the material and to inhalation of fumes. Contact causes burns and dermatitis. Some tars are carcinogenic, and sporadic cases of epithelioma of the neck, forearms, and scrotum have been observed among these workers. The fumes irritate the eyes and respiratory organs, and inhalation over a prolonged period may cause slight anaemia. Bronchial carcinoma may occur. Road-laying, however, is not a dangerous or an unhealthy occupation.

Pitchmastic is a synthetic material which is used mainly in the flooring of huts, kitchens, and similar premises. It was introduced during the war years as a substitute for asphalt and wood. It consists of pitch (14–17%) aggregated with fine limestone or other grit. Heavy tar oils are used as a flux. The material is spread hot and usually by the workman in a kneeling position. In the early days all sorts of waste materials were used in its manufacture, and pitchmastic acquired a reputation for irritant and objectionable fumes. The irritation affected the eyes, skin, and alimentary and respiratory organs. Pitchmastic is still used, but it is controlled by British Standard 1450 (1948). This specifies that "when the pitch, flux and binder are each tested . . . *they shall not produce fumes* . . . which are either irritant or likely to be injurious or offensive to persons employed in the laying of pitchmastic." Accordingly if standard material is used pitchmastic's bad reputation is undeserved. As a general principle, however, workmen who are chesty should not unnecessarily expose themselves to dust or fumes.

### Visiting Small Children

**Q.**—*Some paediatricians consider that the parents of children in this convalescent home should be able to visit their children daily instead of once a week as at present, and on this account do not use the home. They say that up to the age of 7 the amount of grief suffered by a child separated from its mother for more than a few days is equivalent to that which would be caused by her death, and that such deprivation has serious psychological consequences in all cases. What is your expert's opinion?*

**A.**—It is now widely recognized that young children, especially those under 5 years, suffer anxiety and unhappiness if they are away from their mothers (or others to whom they are attached), and that many of them show emotional disturbances after their return home, particularly anxiety about being left and increased jealousy and contrariness. These disturbances sometimes persist for many months, and, if not patiently dealt with, may become permanent. Although it is certainly not true that experiences of this kind have "serious psychological consequences in

all cases," the risk of creating or aggravating psychological difficulties in children under 5 years is real. Unless there are compelling reasons, such children are best not sent for convalescence without their mother or other familiar relative. On the other hand, most children over about 8 years benefit by a holiday away from home. Those of 6 and 7 vary.

Daily visiting for children in hospital has been strongly pressed by the Minister of Health for some years. A Ministry circular to hospitals two years ago (see this *Journal*, February 4, 1956, p. 256) expressed the hope that daily visiting would become the general practice of hospitals which admit children, and is worth consulting.

### Immunity to Measles

**Q.**—*What degree of immunity to measles is conferred on a patient by a primary attack?*

**A.**—Immunity following an attack of measles is, in most cases, solid and long-lasting. Second attacks, well documented by competent clinicians, have occasionally been recorded, but, because of the ready confusion with rubella and other macular eruptions, there is some doubt about the majority of reported second attacks. Most adults who have suffered from measles in childhood still have in their blood specific antibody, on which immunity to the disease seems largely to depend.

### Operative Treatment of Varicose Veins

**Q.**—*What are the latest techniques in the operative treatment of varicose veins? I have been asked about the "English method" in which the veins are "sewed."*

**A.**—The method of treating varicose veins depends upon whether or not there is ulceration. The usual treatment in Britain for varices uncomplicated by ulceration is a long saphenous and, when necessary, a short saphenous stripping operation.[1] In patients with ulceration this stripping operation is augmented by ligature of the ankle perforating veins.[2] The venous drainage of the skin of the ulcer-bearing areas just above the malleoli is largely via the ankle perforating veins to the deep veins and not, as was thought, via the saphenous veins. To cure ulceration and prevent recurrence, therefore, it is usually necessary to tie the ankle perforating veins.

REFERENCES

1 Dodd, H., and Cockett, F. B., *The Pathology and Surgery of the Veins of the Lower Limb*, 1956. Livingstone, Edinburgh.
2 Cockett, F. B., and Jones, D. E. E., *Lancet*, 1953, **1**, 17.

### Paroxysmal Tachycardia and Diuresis

**Q.**—*A man of 72 years with paroxysmal tachycardia which began two years ago has on average two attacks of palpitations a day, each lasting an hour or so. After an attack there is a diuresis of two or three pints of pale urine; between attacks his urinary output is within normal limits. Clinical examination reveals no oedema, B.P. 190/100, regular pulse, and normal heart sounds. What is the explanation of this diuresis?*

**A.**—The attacks of paroxysmal tachycardia which started at the age of 70 are presumably arteriosclerotic in aetiology. In such a patient the rapid ventricular rate during the attacks is associated with a fall in cardiac output, the development of congestive failure, and retention of salt and water in the body. When the attack stops the cardiac output and renal blood flow rapidly return to normal, and the retained salt and water are excreted, thus causing the diuresis noted in the patient. In younger patients in whom the heart is healthy there may be polyuria *during* an attack of paroxysmal tachycardia, provided the ventricular rate is not unduly rapid (less than 180 per minute), as in these circumstances the cardiac output may be increased during an attack.

## NOTES AND COMMENTS

**Inheritance of Congenital Pyloric Stenosis.**—Professor T. McKEOWN (Birmingham) writes: I believe your discussion of the inheritance of congenital pyloric stenosis (January 11, p. 117) contains one of the rare inaccuracies in "Any Questions?" It is stated that, when a man or woman who has recovered from pyloric stenosis has had one affected child, the risk for later children "is probably, but not certainly, increased." So far as I know the only available data[1] suggest that the risk is enormously increased, the proportion of later children affected being approximately 40%.

OUR EXPERT replies: The discrepancy between Professor McKeown's estimate of 40% and my own upper estimate of 1 to 4 (25%) for a boy and 1 in 16 (6%) for a girl seems to be due to two differences of opinion. (1) The query referred to father and children who had had pyloric stenosis confirmed at operation. Since a diagnosis of pyloric stenosis is uncertain, particularly a generation ago, unless confirmed at operation, I thought it best to use only families where parent and child had been treated operatively. This leaves eight families with more than one child in the family from the London series[2] and five from the Birmingham series.[3] (2) All but one of these 13 families were ascertained through affected children and not through affected parents. Professor McKeown's estimate uses a method,[2] which is correct only on the assumption that in these circumstances a family with two affected children is no more likely to come to notice than a family with one affected child. I prefer the assumption that the chance of these families coming to notice was proportional to the number of affected children they contained. On this assumption, the London series gives a risk of 2 in 11 (or 3 in 14 if the family, ascertained through an affected parent, is counted once for each affected child) and the Birmingham series a risk of 1 in 5 (or 2 in 5 if the child medically treated is included). This suggests a risk closer to 20% than 40%. But the margin of error in an estimate from such a small number of families is large, and the findings are compatible perhaps both with no increase beyond the risk where there has been no child already born affected, and the high risk of 40% suggested by Professor McKeown.

REFERENCES

1 McKeown, T., and MacMahon, B., *Arch. Dis. Childh.*, 1955, **30**, 497.
2 Carter, C. O., and Powell, W. B., *Lancet*, 1954, **1**, 746.
3 Hogben, L., *J. Genet.*, 1931, **25**, 97.

**Angular Stomatitis.**—Dr. D. REID TWEEDIE (Perak, Malaya) writes: With reference to the comments on angular stomatitis ("Notes and Comments," December 7, 1957, p. 1382, and "Any Questions?" October 26, 1957, p. 1007), after 25 years' residence in the tropics I found myself suffering from this intractable condition. The fissures resisted the medicaments of some of the best dermatological brains of Harley Street. In the end the fissures disappeared after an antrostomy for a chronic purulent antritis due to an infected tooth, a relic of internment in Singapore during the Japanese occupation of Malaya. Any mild recurrence now disappears rapidly after applying iodochlorhydroxyquin ("vioform") ointment.

**Corrections.**—In the medical memorandum "General Anaesthesia as an Aid to Therapeutic Hypothermia" by Dr. James Parkhouse (*Journal*, September 28, 1957, p. 751), the reference to Rowbotham *et al.* was incorrectly given as *Lancet*, 1957, **1**, 1061. The page number should have been 1016.

We regret an error in Professor H. L. Marriott's letter on "Post-operative Position" (*Journal*, January 25, p. 215). The third word of line 5 of the second column should have been "sacrum," not "sternum."

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